The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2015 VOL. 373 NO. 23

Trial of Continuous or Interrupted Chest Compressions during CPR

Graham Nichol, M.D., M.P.H., Brian Leroux, Ph.D., Henry Wang, M.D., Clifton W. Callaway, M.D., Ph.D., George Sopko, M.D., Myron Weisfeldt, M.D., Ian Stiell, M.D., Laurie J. Morrison, M.D., Tom P. Aufderheide, M.D., Sheldon Cheskes, M.D., Jim Christenson, M.D., Peter Kudenchuk, M.D., Christian Vaillancourt, M.D., Thomas D. Rea, M.D., Ahamed H. Idris, M.D., Riccardo Colella, D.O., M.P.H., Marshal Isaacs, M.D., Ron Straight, Shannon Stephens, Joe Richardson, Joe Condle, Robert H. Schmicker, M.S., Debra Egan, M.P.H., B.S.N., Susanne May, Ph.D., and Joseph P. Ornato, M.D., for the ROC Investigators*

ABSTRACT

BACKGROUND

During cardiopulmonary resuscitation (CPR) in patients with out-of-hospital cardiac arrest, the interruption of manual chest compressions for rescue breathing reduces blood flow and possibly survival. We assessed whether outcomes after continuous compressions with positive-pressure ventilation differed from those after compressions that were interrupted for ventilations at a ratio of 30 compressions to two ventilations.

METHODS

This cluster-randomized trial with crossover included 114 emergency medical service (EMS) agencies. Adults with non–trauma-related cardiac arrest who were treated by EMS providers received continuous chest compressions (intervention group) or interrupted chest compressions (control group). The primary outcome was the rate of survival to hospital discharge. Secondary outcomes included the modified Rankin scale score (on a scale from 0 to 6, with a score of ≤3 indicating favorable neurologic function). CPR process was measured to assess compliance.

RESULTS

Of 23,711 patients included in the primary analysis, 12,653 were assigned to the intervention group and 11,058 to the control group. A total of 1129 of 12,613 patients with available data (9.0%) in the intervention group and 1072 of 11,035 with available data (9.7%) in the control group survived until discharge (difference, −0.7 percentage points; 95% confidence interval [CI], −1.5 to 0.1; P=0.07); 7.0% of the patients in the intervention group and 7.7% of those in the control group survived with favorable neurologic function at discharge (difference, −0.6 percentage points; 95% CI, −1.4 to 0.1, P=0.09). Hospital-free survival was significantly shorter in the intervention group than in the control group (mean difference, −0.2 days; 95% CI, −0.3 to −0.1; P=0.004).

CONCLUSIONS

In patients with out-of-hospital cardiac arrest, continuous chest compressions during CPR performed by EMS providers did not result in significantly higher rates of survival or favorable neurologic function than did interrupted chest compressions. (Funded by the National Heart, Lung, and Blood Institute and others; ROC CCC ClinicalTrials.gov number, NCT01372748.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Nichol at Box 359727, 325 Ninth Ave., Seattle, WA 98104, or at nichol@uw.edu.

*A complete list of the Resuscitation Outcomes Consortium (ROC) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 9, 2015, at NEJM.org.

N Engl J Med 2015;373:2203-14.
DOI: 10.1056/NEJMoa1509139

Standard cardiopulmonary resuscitation (CPR) consists of manual chest compressions to maintain blood flow and positive-pressure ventilation to maintain oxygenation until spontaneous circulation is restored.[1] Chest compressions are interrupted frequently by ventilations given as rescue breathing during the treatment of out-of-hospital cardiac arrest.[2-4] These interruptions reduce blood flow and potentially reduce the effectiveness of CPR.[5] One strategy to reduce the interruption of compressions is to provide asynchronous positive-pressure ventilation while not pausing for ventilations.

The interruption of chest compressions has been associated with decreased survival in animals with cardiac arrest.[6] In nonasphyxial arrest, continuous compressions were as effective as compressions that were interrupted for ventilations of 4 seconds in duration.[5] Also, the use of continuous compressions resulted in significantly better neurologic function than that with compressions that included longer interruptions for ventilations.[6] In contrast, in asphyxial arrest, ventilation improved outcomes.[7] Observational studies involving humans with out-of-hospital cardiac arrest of presumed cardiac cause have suggested that continuous compressions are associated with higher rates of survival than interrupted compressions.[8,9] We tested whether continuous chest compressions, as compared with chest compressions interrupted for ventilation, during CPR performed by emergency medical service (EMS) providers affected the rate of survival, neurologic function, or the rate of adverse events.

Methods

Study Design and Oversight

A detailed description of the design of the trial has been published previously.[10] The trial was conducted by the Resuscitation Outcomes Consortium (ROC). This network includes 10 clinical sites in North America that have experience conducting randomized trials involving patients with out-of-hospital cardiac arrest; the network also includes the regional EMS agencies associated with these sites and a central coordinating center in Seattle.[11-13] Eight ROC sites and 114 EMS agencies participated in this trial (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Applicable institutional review boards approved the conduct of this study; the requirement for informed consent was waived because the study involved research in emergency medicine. Patients or their legally authorized representatives were informed of participation after the event.

The trial was sponsored by the National Heart, Lung, and Blood Institute, the Canadian Institutes of Health Research, and others (see the Supplementary Appendix). The investigators, including two authors who are employees of the National Institutes of Health, designed and conducted the study, analyzed the data, interpreted the results, wrote the manuscript, and made the decision to submit the manuscript for publication. The trial statisticians had full access to all the data in the study and take responsibility for the integrity of the data, the completeness and accuracy of the data and analyses, and the fidelity of this report to the trial protocol, available at NEJM.org.

Patient Population

The trial included adults with non–trauma-related out-of-hospital cardiac arrest who received chest compressions performed by providers from participating EMS agencies who were dispatched to the scene. Patients were excluded if they had an EMS-witnessed arrest, a written advance directive to not resuscitate, a traumatic injury, an asphyxial cause of arrest, uncontrolled bleeding or exsanguination, known pregnancy, or preexisting tracheostomy; were known to be prisoners; had initial CPR performed by a nonparticipating EMS provider; were treated with a mechanical chest-compression device before manual CPR by ROC EMS personnel; had advanced airway management before ROC EMS agency arrival; or had, a priori, opted not to participate in resuscitation research. Some patients were co-enrolled in a trial of antiarrhythmic therapy for recurrent ventricular fibrillation.[14]

Study Interventions

The trial used cluster randomization with crossovers. The 114 participating EMS agencies across the eight participating ROC sites were grouped into 47 clusters. Clusters of agencies were randomly assigned, in a 1:1 ratio, to perform continuous chest compressions or interrupted chest compressions during all the out-of-hospital cardiac arrests to which they responded. Twice per

year, each cluster was crossed over to the other resuscitation strategy. The pattern of randomized cluster assignments is shown in Figure S1 in the Supplementary Appendix.

The trial required each cluster of EMS agencies to begin by enrolling patients in a run-in phase to demonstrate adherence to the protocol. Once a cluster demonstrated proficiency with the given treatment by meeting prespecified performance and compliance benchmarks as determined by an internal study monitoring committee, they were entered into the active-enrollment phase. Benchmarks included adherence to randomized treatment-group assignment, timeliness and completion of data entry, and availability of CPR-process measures recorded by the monitor–defibrillator. Details of the randomization and run-in procedures are provided in the Supplementary Appendix.

Patients assigned to the group that received continuous chest compressions (intervention group) were to receive continuous chest compressions at a rate of 100 compressions per minute, with asynchronous positive-pressure ventilations delivered at a rate of 10 ventilations per minute. Patients assigned to the group that received interrupted chest compressions (control group) were to receive compressions that were interrupted for ventilations at a ratio of 30 compressions to two ventilations; ventilations were to be given with positive pressure during a pause in compressions of less than 5 seconds in duration. Details of the CPR protocol, airway management, and use of pressors are provided in the Supplementary Appendix text and in Figures S2 and S3 in the Supplementary Appendix. Hospital-based care, including targeted temperature management, was monitored but was not standardized in this trial.

CPR-PROCESS MONITORING

Study sites were required to acquire and report CPR-process data before beginning enrollment and throughout the trial period. Process data were measured by commercially available monitor–defibrillators during attempted resuscitation. Study-site coordinators were instructed to audit these data for accuracy. In addition, an internal study monitoring committee, whose members were unaware of the treatment outcomes, periodically reviewed these data. Their goal was to assess whether prespecified targets for performance were met for measures such as enrollment rate, treatment-adherence rate, and key elements of concurrent care and then to make recommendations regarding steps to be implemented to increase these rates.[10] Details are provided in the Supplementary Appendix.

OUTCOMES

The primary outcome was the rate of survival to hospital discharge. Secondary outcomes included neurologic function at discharge, which was measured with the use of the modified Rankin scale (scores range from 0, indicating no symptoms, to 6, indicating death, with a score of ≤3 indicating favorable neurologic function) on the basis of review of the clinical record, and adverse events. Hospital-free survival was defined as the number of days alive and permanently out of the hospital during the first 30 days after the cardiac arrest. Other outcomes were collected for descriptive purposes. Detailed descriptions of the study outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that 23,600 patients (11,800 patients per group) would need to be enrolled for the study to have 90% power to detect a rate of survival to discharge of 8.1% in the control group versus 9.4% in the intervention group, at an overall two-sided alpha level of 0.05. The estimated survival rate in the control group was based on data from the ROC Prehospital Resuscitation Impedance Valve and Early versus Delayed Analysis (ROC PRIMED) trial.[12,13]

The effectiveness population included all the patients who received the randomly assigned treatment during the active-enrollment phase of the study. The safety population included all the patients who received the randomly assigned treatment during either the run-in phase or the active-enrollment phase. The primary test of the null hypothesis used a difference in event rates divided by the estimated robust standard errors that were based on the Huber–White sandwich estimator.[15,16] The 95% confidence intervals were calculated with adjustment for interim analyses. The comparisons of the treatment groups with respect to the distribution of the secondary outcomes used robust standard errors but were not adjusted for interim analyses. An independent data and safety monitoring board monitored trial

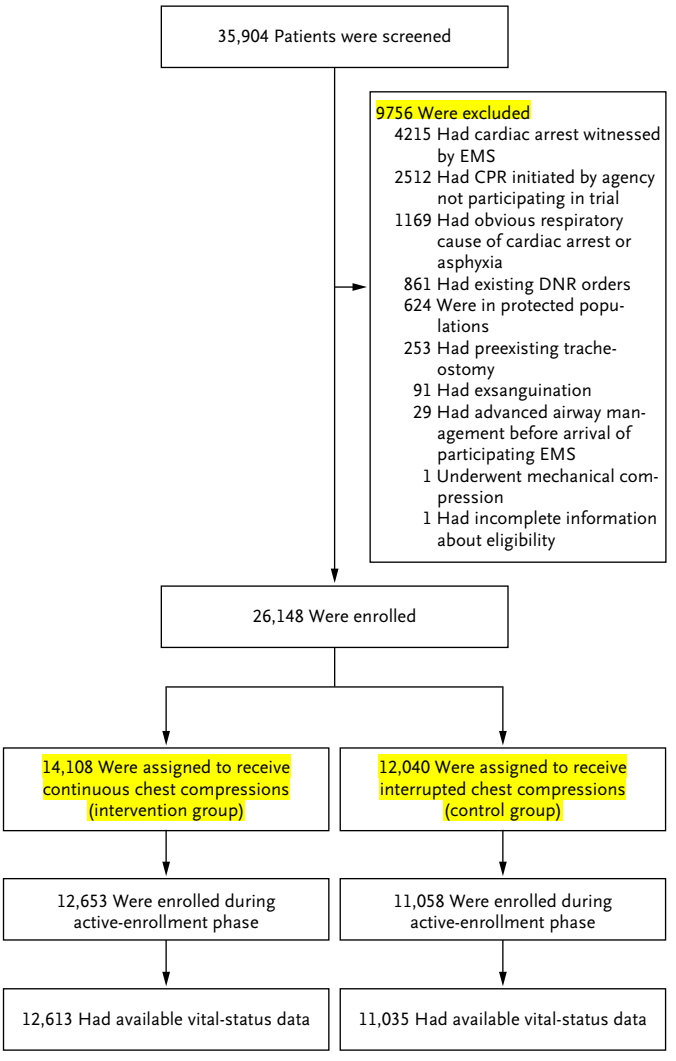

Figure 1. Screening and Randomization of the Patients.

Protected populations included children, pregnant women, and prisoners. CPR denotes cardiopulmonary resuscitation, DNR do not resuscitate, and EMS emergency medical service.

progress and safety with the use of formal stopping boundaries; interim analyses were performed every 6 months.

The effect of treatment on the primary and secondary outcomes within subgroups that were defined according to the presence or absence of prognostic factors was examined separately, as detailed in the Supplementary Appendix. Tests for interaction were performed. The effect of treatment was also examined in two per-protocol analyses in per-protocol populations that were defined on the basis of CPR-process data. The first per-protocol analysis used an automated algorithm to define adherence to CPR process (Table S1 in the Supplementary Appendix), and the second was based on the assessment of CPR-process data by the research coordinator. In addition, multiple hot-deck imputation was used to account for missing vital-status data at discharge.[17] Further details regarding the statistical analyses are provided in the Supplementary Appendix.

RESULTS

ENROLLMENT, RANDOMIZATION, AND CHARACTERISTICS OF THE PATIENTS

The first EMS agency entered the run-in phase on June 6, 2011. All the study sites stopped enrollment on May 28, 2015, when the maximum expected enrollment was achieved. Of 35,904 patients with out-of-hospital cardiac arrest who were screened, 26,148 were eligible for participation in the trial and were enrolled in the trial during either the run-in phase or the active-enrollment phase (Fig. 1). The active-enrollment phase included 23,711 patients, of whom 12,653 were assigned to the intervention group and 11,058 to the control group. Data regarding the primary outcome were available for 12,613 patients (99.7%) in the intervention group and for 11,035 (99.8%) in the control group.

The characteristics of the patients before and after the initiation of the randomly assigned treatment, as well as the characteristics of the EMS providers and the hospital treatments, were generally well balanced between the groups, with some small differences that were not considered to be clinically significant (Tables 1 and 2). EMS providers achieved small but important intended differences in CPR process (chest-compression fraction, number of pauses in compressions, and pause length) between the treatment groups (Table 2, and Fig. S4 in the Supplementary Appendix).

The per-protocol population that was determined by application of an automated algorithm to the CPR-process data excluded 6108 patients in the intervention group and 7371 in the control group. In this per-protocol population, the characteristics of the patients and characteristics of the EMS providers after treatment were imbalanced, with significantly higher rates of a shock-

Table 1. Pretreatment Characteristics of the Patients Included in the Effectiveness Population.*

Characteristic	Intervention Group (N=12,653)	Control Group (N=11,058)
Age — yr	66.4±17.2	66.2±17.0
Male sex — no. (%)	8029 (63.5)	7126 (64.4)
Obvious cause of cardiac arrest — no./total no. (%)†	397/12,650 (3.1)	355/11,058 (3.2)
Arrest occurring in public location — no./total no. (%)	1797/12,632 (14.2)	1642/11,049 (14.8)
Witness status — no./total no. (%)		
Bystander witnessed	5179/12,318 (42.0)	4725/10,852 (43.5)
Not witnessed	7139/12,318 (58.0)	6127/10,852 (56.5)
Bystander-initiated CPR — no./total no. (%)		
Yes	5859/12,491 (46.9)	5129/10,901 (47.1)
No	6632/12,491 (53.1)	5772/10,901 (52.9)
Time from dispatch to first arrival of EMS		
Mean — min	5.9±2.5	5.9±2.6
≤4 min — no./total no. (%)	2521/12,424 (20.3)	2272/10,851 (20.9)
Advanced life support at the scene		
Receipt of advanced life support — no. (%)	12,286 (97.1)	10,741 (97.1)
Time from dispatch to first arrival of advanced life support — min	9.0±5.1	9.0±5.1
Study site — %‡		
A	47.6	52.4
B	50.7	49.3
C	56.0	44.0
D	54.9	45.1
E	51.6	48.4
F	50.4	49.6
G	55.8	44.2
H	50.5	49.5

* Plus–minus values are means ±SD. The effectiveness population included all the patients who received the randomly assigned treatment during the active-enrollment phase of the study. The intervention group included patients who received continuous chest compressions, and the control group those who received interrupted chest compressions. There were no significant between-group differences at the significance level of 0.05 except for witness status (P=0.005) and study site (P<0.001). Data on age were missing for 6 patients in the intervention group and 10 in the control group, data on time from dispatch to first EMS arrival were missing for 229 patients in the intervention group and 207 in the control group, and data on time from dispatch to first arrival of advanced life support were missing for 403 patients in the intervention group and 319 in the control group. CPR denotes cardiopulmonary resuscitation, and EMS emergency medical service.

† Obvious causes of cardiac arrest included but were not limited to drug poisoning and terminal illness.

‡ The eight study sites are listed in a different order than the order shown in another table, in order to conceal the identity of the sites and protect sensitive data regarding the EMS agencies.

able rhythm and prehospital intubation in the control group than in the intervention group (Table S2 in the Supplementary Appendix).

PRIMARY AND SECONDARY OUTCOMES

During the active-enrollment phase, 1129 of 12,613 patients (9.0%) in the intervention group (which received continuous chest compression) and 1072 of 11,035 (9.7%) in the control group (which received interrupted chest compressions) survived to hospital discharge (difference with adjustment for cluster and sequential monitoring, −0.7 percentage points; 95% confidence interval [CI], −1.5 to 0.1; P=0.07) (Table 3). Among

Table 2. Post-Treatment Characteristics and Treatments Received by Patients in the Effectiveness Population.*

Characteristic	Intervention Group (N=12,653)	Control Group (N=11,058)	P Value
Time between arrival of EMS and start of CPR			
Mean — min	2.4±2.1	2.4±2.2	0.33
≤10 min — no./total no. (%)	11,155/11,256 (99.1)	9880/9969 (99.1)	0.97
First rhythm — no./total no. (%)			0.71
Ventricular tachycardia, ventricular fibrillation, or shockable	2,836/12,651 (22.4)	2501/11,056 (22.6)	
Nonshockable	9,640/12,651 (76.2)	8406/11,056 (76.0)	
Unknown, could not be determined, or not available	175/12,651 (1.4)	149/11,056 (1.3)	
No. of shocks, if given	3.4±3.2	3.4±3.0	0.69
Prehospital intubation — no./total no. (%)†			
Attempted	7,195/12,653 (56.9)	6428/11,058 (58.1)	0.32
Successful	6,042/7195 (84.0)	5438/6428 (84.6)	0.35
CPR-process measures taken for ≤6 min or until return of spontaneous circulation, whichever occurred first			
Chest-compression fraction‡	0.83±0.14	0.77±0.14	<0.001
Median	0.90	0.82	
Interquartile range	0.82–0.96	0.74–0.89	
No. of pauses >2 sec	3.8±2.6	7.0±4.3	<0.001
Compression rate — no. of compressions/min	110±11	109±12	0.82
Compression depth — mm	48±12	49±12	0.03
Pause — sec			
Before shock	12±10	12±11	0.70
After shock	6±9	6±14	0.47
Drugs administered before arrival at hospital			
Epinephrine — no./total no. (%)	10,351/12,631 (81.9)	9048/11,042 (81.9)	0.99
Dose — mg§	3.8±2.0	3.8±2.1	0.92
Bicarbonate — no./total no. (%)	2,551/12,628 (20.2)	2351/11,035 (21.3)	0.37
Atropine — no./total no. (%)	503/12,628 (4.0)	389/11,035 (3.5)	0.56
Lidocaine — no./total no. (%)	246/12,629 (1.9)	229/11,034 (2.1)	0.46
Amiodarone — no./total no. (%)	561/12,629 (4.4)	541/11,034 (4.9)	0.37
Vasopressin — no./total no. (%)	164/12,630 (1.3)	187/11,038 (1.7)	0.29
Co-enrollment in ALPS study			
Enrolled — no. (%)	1228 (9.7)	1115 (10.1)	0.56
Group A — no./total no. (%)	416/1,228 (33.9)	377/1,115 (33.8)	
Group B — no./total no. (%)	410/1,228 (33.4)	370/1,115 (33.2)	
Group C — no./total no. (%)	402/1,228 (32.7)	368/1,115 (33.0)	
Not enrolled — no. (%)	11,425 (90.3)	9943 (89.9)	

Table 2. (Continued.)

Characteristic	Intervention Group (N=12,653)	Control Group (N=11,058)	P Value
Hospital procedures — no./total no. (%)¶			
Hypothermia	1,692/3108 (54.4)	1502/2860 (52.5)	0.18
Coronary catheterization <24 hr after ED arrival	916/3108 (29.5)	882/2860 (30.8)	0.20
Implantable cardioverter–defibrillator	293/3108 (9.4)	306/2860 (10.7)	0.13

* Plus–minus values are means ±SD. Data on time between arrival of EMS to start of CPR were missing for 1397 patients in the intervention group and 1089 in the control group, data on the chest-compression fraction were missing for 2612 patients in the intervention group and 2103 in the control group, data on the number of pauses lasting more than 2 sec were missing for 2878 patients in the intervention group and 2249 in the control group, data on the compression rate were missing for 1430 patients in the intervention group and 1261 in the control group, data on the compression depth were missing for 6164 patients in the intervention group and 5734 in the control group, data on pause before shock were missing for 1135 patients in the intervention group and 1209 in the control group, data on pause after shock were missing for 1213 patients in the intervention group and 1262 in the control group, and data on the epinephrine dose were missing for 23 patients in the intervention group and 23 in the control group. ALPS denotes Amiodarone, Lidocaine, or Placebo Study (ClinicalTrials.gov number, NCT01401647), and ED emergency department.

† Some EMS agencies were able to report attempted intubation and others successful intubation. The denominators differ owing to missing data.

‡ The chest-compression fraction is the proportion of each minute during which compressions were given.

§ Values are for patients who received epinephrine.

¶ Values are for patients admitted as in-patients to the hospital.

patients with available data on neurologic status, 883 of 12,560 patients (7.0%) in the intervention group and 844 of 10,995 (7.7%) in the control group survived with a modified Rankin scale score of 3 or less (difference with adjustment for cluster, −0.6 percentage points; 95% CI, −1.4 to 0.1; P=0.09). Patients in the intervention group were significantly less likely than those in the control group to be transported to the hospital (difference, −2.0 percentage points; 95% CI, −3.6 to −0.5; P=0.01) or admitted to the hospital (difference, −1.3 percentage points; 95% CI, −2.4 to −0.2; P=0.03). Hospital-free survival was significantly shorter in the intervention group than in the control group (mean difference, −0.2 days; 95% CI, −0.3 to −0.1; P=0.004).

In the per-protocol population, the survival rate was significantly lower in the intervention group, which included 6529 patients, than in the control group, which included 3678 patients (adjusted difference, −2.0 percentage points; 95% CI, −2.9 to −1.1; P<0.001). After the imputation of missing outcomes (for 40 patients [0.3%] in the intervention group and for 23 [0.2%] in the control group), the overall difference in the survival rate between the treatment groups in the effectiveness population was still not significant. Adjustment for pretreatment confounders attenuated the difference in the survival rate between the treatment groups (difference, −0.3 percentage points; 95% CI, −1.1 to 0.4; P=0.38).

ADDITIONAL ANALYSES

There were a few nominally significant between-group differences in the prespecified pretreatment subgroups (Table 4). There was nominal heterogeneity of treatment effect that was related to witnessed status (P=0.05 for interaction), and individual case adherence to performance benchmarks (P=0.05 for interaction). There was also nominal heterogeneity of treatment effect that was related to the timing of insertion of an advanced airway (P=0.04 for interaction), but the distribution of such patients was unbalanced between the treatment groups (Table S3 in the Supplementary Appendix). There was no significant relationship between the difference in survival rate between the treatment groups and the incidence of favorable neurologic status in the control group according to clinical site (Fig. S5 in the Supplementary Appendix). There was no significant difference between the two treatment groups in the rates of individual adverse events (Table S4 in the Supplementary Appendix)

Table 3. Outcomes in Patients Included in the Primary Analysis.*

Outcome	Intervention Group (N=12,653)	Control Group (N=11,058)	Adjusted Difference (95% CI)	P Value
Effectiveness population				
Primary outcome: survival to discharge — no./total no. (%)	1,129/12,613 (9.0)	1072/11,035 (9.7)	−0.7 (−1.5 to 0.1)	0.07
Transport to hospital — no. (%)	6686 (52.8)	6066 (54.9)	−2.0 (−3.6 to −0.5)	0.01
Return of spontaneous circulation at ED arrival — no./total no. (%)	3,058/12,646 (24.2)	2799/11,051 (25.3)	−1.1 (−2.4 to 0.1)	0.07
Admission to hospital — no./total no. (%)	3,108/12,653 (24.6)	2860/11,058 (25.9)	−1.3 (−2.4 to −0.2)	0.03
Survival to 24 hr — no./total no. (%)	2,816/12,614 (22.3)	2569/11,031 (23.3)	−1.0 (−2.1 to 0.2)	0.10
Hospital-free survival — days†	1.3±5.0	1.5±5.3	−0.2 (−0.3 to −0.1)	0.004
Discharge home — no./total no. (%)	844/12,613 (6.7)	794/11,034 (7.2)	−0.5 (−1.2 to 0.2)	0.15
Modified Rankin scale score‡				
≤3 — no./total no. (%)	883/12,560 (7.0)	844/10,995 (7.7)	−0.6 (−1.4 to 0.1)	0.09
Mean	5.63±1.29	5.60±1.35	0.04 (0.0 to 0.08)	0.04
Distribution — no./total no. (%)				
0	320/12,560 (2.5)	336/10,995 (3.1)	—	—
1	271/12,560 (2.2)	222/10,995 (2.0)	—	—
2	147/12,560 (1.2)	161/10,995 (1.5)	—	—
3	145/12,560 (1.2)	125/10,995 (1.1)	—	—
4	97/12,560 (0.8)	103/10,995 (0.9)	—	—
5	98/12,560 (0.8)	87/10,995 (0.8)	—	—
6	11,482/12,560 (91.4)	9961/10,995 (90.6)	—	—
Adjusted analyses of primary outcome				
Adjusted for study site	—	—	−0.6 (−1.3 to 0.1)	0.09
Adjusted for age	—	—	−0.7 (−1.5 to 0.1)	0.07
Adjusted for sex	—	—	−0.7 (−1.5 to 0.1)	0.07
Adjusted for public location	—	—	−0.7 (−1.4 to 0.1)	0.09
Adjusted for bystander-witnessed	—	—	−0.6 (−1.4 to 0.3)	0.18
Adjusted for bystander-initiated CPR	—	—	−0.7 (−1.5 to 0.0)	0.07
Adjusted for duration until EMS arrival	—	—	−0.7 (−1.5 to 0.0)	0.07
Adjusted for all the above covariates	—	—	−0.3 (−1.1 to 0.4)	0.38
Additional analyses of primary outcome				
Analysis including multiple imputation — %	9.0	9.8	−0.7 (−1.5 to 0.1)	0.07
Prespecified per-protocol analysis				
Treatment determined by automated algorithm — no./total no. (%)	497/6529 (7.6)	353/3678 (9.6)	−2.0 (−2.9 to −1.1)	<0.001
Adjusted analysis§	—	—	−1.3 (−2.5 to −0.1)	0.04
Post hoc per-protocol analysis: treatment determined by coordinator assessment — no./total no. (%)	834/9649 (8.6)	606/6156 (9.8)	−1.2 (−2.0 to −0.4)	<0.01

Table 3. (Continued.)

Outcome	Intervention Group (N=12,653)	Control Group (N=11,058)	Adjusted Difference (95% CI)	P Value
Safety population				
Total no.	14,065	12,015		
Survival to discharge — no. (%)	1273 (9.1)	1152 (9.6)	–0.5 (–1.3 to 0.2)	0.15

* Plus–minus values are means ±SD. Differences between percent values are shown in percentage points. Difference, confidence intervals, and P values for the analysis in the effectiveness population were adjusted for cluster and sequential monitoring; other analyses were adjusted for cluster only. Data on hospital-free survival were missing for 92 patients in the intervention group and 70 in the control group, and data on the modified Rankin scale score were missing for 93 patients in the intervention group and 63 in the control group. ED denotes emergency department.

† Hospital-free survival was defined as the number of days alive and permanently out of the hospital during the first 30 days after the cardiac arrest.

‡ Scores on the modified Rankin scale range from 0, indicating no symptoms, to 6, indicating death; a score of 3 or less indicates favorable neurologic function.

§ The analysis was adjusted for site, age, sex, public location, bystander-witnessed cardiac arrest, bystander-initiated CPR, and time from EMS dispatch to arrival.

or in the time to death or awakening (Fig. S6 in the Supplementary Appendix).

DISCUSSION

In this large randomized trial involving adults with out-of-hospital cardiac arrest, a strategy of continuous manual chest compressions with positive-pressure ventilation was not associated with a significantly higher rate of survival to discharge or favorable neurologic function than a strategy of manual chest compressions with interruptions for ventilation performed by EMS providers. The group assigned to receive continuous chest compressions had significantly lower rates of transport to the hospital and admission to the hospital, as well as shorter hospital-free survival, than the group assigned to receive interrupted chest compressions. In the per-protocol analyses, patients who received continuous chest compressions had significantly lower survival rates than those who received compressions with interruptions.

Previous observational studies have shown large increases in survival rates among patients with a shockable rhythm[9,18-20] with the implementation of continuous compressions by EMS providers versus compressions interrupted for ventilations. Among patients with a noncardiac cause of cardiac arrest who were treated by laypersons[21] or those with a nonshockable rhythm who were treated by EMS providers,[9] continuous compressions were not associated with a significant improvement in outcome. In these previous studies, participating EMS agencies did not measure CPR process when implementing continuous compressions, and implementation occurred simultaneously with other changes, including directions to give intravenous epinephrine early, to use a nonrebreather mask with passive ventilation, to defer airway insertion, and to reduce the number of defibrillations given with each rhythm analysis. In the initial reports of implementation of continuous compressions,[9,20] most patients received rescue breathing by means of positive-pressure ventilation with a bag-valve mask. Other interventions that each patient received were not reported. It seems plausible that some of the observed improvement in these previous studies was due to improved CPR process (e.g., compression rate and depth), concurrent improvements in the system of care, or Hawthorne effects (changes in behavior resulting from awareness of being observed)[22] rather than to the implementation of continuous compressions alone.

We collected CPR-process data on 90% of all the patients and described the pattern of CPR in each group. Overall, the quality of CPR that was delivered to patients was consistent with contemporary evidence-based practice guidelines.[1,23]

Table 4. Prespecified Subgroup Analyses of the Primary Outcome in the Effectiveness Population.*

Subgroup	Intervention Group (N = 12,653)	Control Group (N = 11,058)	Difference (95% CI)	P Value
First rhythm — no./total no. (%)				0.34
Ventricular tachycardia, ventricular fibrillation, or shockable	780/2813 (27.7)	739/2487 (29.7)	−2.0 (−4.6 to 0.6)	
Nonshockable	289/9623 (3.0)	288/8397 (3.4)	−0.4 (−1.0 to 0.1)	
Unknown, could not be determined, or not available	60/177 (33.9)	45/151 (29.8)	4.1 (−6.6 to 14.8)	
Witnessed status — no./total no. (%)				0.05
Bystander witnessed	805/5153 (15.6)	812/4707 (17.3)	−1.6 (−3.4 to 0.1)	
Unwitnessed	294/7125 (4.1)	240/6122 (3.9)	0.2 (−0.4 to 0.8)	
Location of arrest — no./total no. (%)				0.77
Public	413/1777 (23.2)	395/1629 (24.2)	−1.0 (−3.9 to 1.9)	
Private	714/10,816 (6.6)	676/9397 (7.2)	−0.6 (−1.2 to 0.0)	
Cause of arrest — no./total no. (%)				0.14
Obvious	1060/12,215 (8.7)	1020/10,680 (9.6)	−0.9 (−1.6 to −0.1)	
Not obvious	69/395 (17.5)	52/355 (14.6)	2.8 (−2.3 to 7.9)	
Bystander-initiated CPR — no./total no. (%)				0.10
Administered	680/5834 (11.7)	663/5113 (13.0)	−1.3 (−2.6 to 0.0)	
Not administered	436/6617 (6.6)	390/5766 (6.8)	−0.2 (−0.9 to 0.5)	
Individual case compliance with performance benchmarks — no./total no. (%)				0.05
Compliance with all benchmarks	361/4077 (8.9)	280/2655 (10.5)	−1.7 (−2.8 to −0.6)	
Noncompliance with ≥1 benchmark	768/8536 (9.0)	792/8380 (9.5)	−0.5 (−1.3 to 0.4)	
Cluster probationary status — no./total no. (%)				0.71
Never on probation	114/785 (14.5)	115/810 (14.2)	0.3 (−2.4 to 3.0)	
On probation at some time but not suspended	984/11,372 (8.7)	928/9849 (9.4)	−0.8 (−1.6 to 0.0)	
Suspended	31/456 (6.8)	29/376 (7.7)	−0.9 (−2.6 to 0.7)	
Study site — %†				0.91
N	12.5	12.1	0.3 (−1.6 to 2.3)	
O	6.7	7.8	−1.1 (−2.4 to 0.1)	
P	18.7	18.8	−0.1 (−2.6 to 2.3)	
Q	8.6	9.0	−0.4 (−4.1 to 3.3)	
R	9.2	9.8	−0.6 (−2.6 to 1.4)	
S	8.3	10.0	−1.7 (−4.3 to 0.9)	
T	7.0	7.0	0.0 (−2.0 to 2.0)	
U	3.0	4.1	−1.1 (−5.4 to 3.2)	
Survival according to timing in treatment period — no./total no. (%)‡				0.38
First 3 mo	582/6434 (9.0)	509/5382 (9.5)	−0.4 (−1.6 to 0.7)	
Second 3 mo	547/6179 (8.9)	563/5653 (10.0)	−1.1 (−2.2 to −0.1)	

* Numbers may differ from those in other tables owing to missing final data regarding vital status. Differences between percent values are shown in percentage points; values may not sum as expected owing to rounding. P values are for interaction.
† The eight study sites are listed in a different order than the order shown in another table, in order to conceal the identity of the sites and protect sensitive data regarding the EMS agencies.
‡ The first 3 months of the treatment period was defined as either May through July or November through January; the second 3 months was defined as either August through October or February through April.

However, the per-protocol analysis, which used an automated algorithm to assess adherence to the CPR process, excluded many trial participants. Often, these exclusions occurred because the automated algorithm could not classify patients as having received either continuous chest compressions or interrupted chest compressions. In a post hoc per-protocol analysis with classification according to assessment by the study coordinator, more patients could be classified, but many patients were still not classified as having received the assigned intervention. These are important limitations of the trial.

In the per-protocol analyses, more patients in the group assigned to receive interrupted compressions than in the group assigned to receive continuous compressions were excluded. There were some between-group imbalances in the characteristics of the patients and treatments. As a consequence, the observation that the survival rate was higher with interrupted chest compressions than with continuous chest compressions was subject to confounding by between-group differences. An adjusted per-protocol analysis corrected for measured differences at baseline but could not correct for unmeasured or post-treatment factors that may have influenced the outcome.

Our study has some other limitations. First, the mean difference in the chest-compression fraction (the proportion of each minute during which compressions were given) between the treatment groups during the trial was small. Differences in chest-compression fraction may be associated with outcome.[3,4] It is possible that in EMS practice outside the context of a clinical trial a larger difference in chest-compression fraction would have occurred and would have been associated with a larger difference in outcome than was observed in this trial.

Second, there was some imbalance in the number of patients assigned to each group in our trial owing to variation in the amount of time during the first cluster period before crossover, an uneven number of cluster periods, and the suspension of a few EMS agencies by the study monitoring committee. There were also some between-group differences in the characteristics of the patients and in the EMS treatment received. Post hoc adjustment for these differences attenuated the difference in the survival rates between the treatment groups (Table S3 in the Supplementary Appendix).

Third, the quality of postresuscitation care, including the use of targeted temperature management[24,25] and early coronary angiography,[25-27] is associated with outcome after out-of-hospital cardiac arrest. We measured but did not mandate postresuscitation care, which may have influenced the rate of survival from admission to discharge.

Finally, we did not measure oxygenation or minutes of ventilation delivered. Low or high oxygen flow is achievable with nonrebreather masks, such as those that were used in prior observational studies of continuous compressions.[28,29] High or low oxygenation and hyperventilation are associated with poor outcome in humans with cardiac arrest.[30-32] We do not know whether there were important differences in oxygenation or ventilation between the two treatment strategies.

In conclusion, among patients with out-of-hospital cardiac arrest in whom CPR was performed by EMS providers, a strategy of continuous chest compressions with positive-pressure ventilation did not result in significantly higher rates of survival or favorable neurologic status than the rates with a strategy of chest compressions interrupted for ventilation.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Supported by multiple cooperative agreements (5U01 HL077863, to the University of Washington Data Coordinating Center; HL077866, to the Medical College of Wisconsin; HL077867, to the University of Washington; HL077871, to the University of Pittsburgh; HL077872, to St. Michael's Hospital; HL077881, to the University of Alabama at Birmingham; HL077885, to the Ottawa Hospital Research Institute; and HL077887, to the University of Texas Southwestern Medical Center) from the National Heart, Lung, and Blood Institute in partnership with the U.S. Army Medical Research and Materiel Command, the Canadian Institutes of Health Research, Institute of Circulatory and Respiratory Health, Defence Research and Development Canada, the Heart and Stroke Foundation of Canada, and the American Heart Association. The Medic One Foundation provided salary support to Dr. Nichol.

Dr. Nichol reports receiving travel support from Abiomed and grant support from Cardiac Science, HeartSine Technologies, Philips Healthcare, Physio-Control, ZOLL Medical, Sotera Wireless, and neuroproteXeon; Dr. Callaway, holding patents related to devices, systems, and methods of characterization of and treatment for ventricular fibrillation (U.S. patent no., 7,444,179), a method and apparatus for selectively defibrillating a patient (U.S. patent no., 6,438,419), and benzoquinoid ansamycins for the treatment of cardiac arrest and stroke (U.S. patent no., 6,174,875); Dr. Cheskes, receiving lecture fees from ZOLL Medical and Physio-Control; and Dr. Idris, receiving grant support from HeartSine Technologies. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the University of Washington–Harborview Center for Prehospital Emergency Care (G.N.) and Clinical Trial Center (G.N., B.L., R.H.S., S.M.) and Seattle–King County Center for Resuscitation Research, University of Washington (P.K., T.D.R.) — all in Seattle; University of Alabama School of Medicine (H.W., S.S.) and Birmingham Fire and Rescue Service (J.R.) — both in Birmingham; Pittsburgh Resuscitation Network, University of Pittsburgh, Pittsburgh (C.W.C., J. Condle); National Heart, Lung, and Blood Institute, Bethesda (G.S., D.E.), and Johns Hopkins University School of Medicine, Baltimore (M.W.) — both in Maryland; Ottawa/Ontario Prehospital Advanced Life Support Resuscitation Outcomes Consortium, Ottawa Hospital Research Institute, University of Ottawa, Ottawa (I.S., C.V.), Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto (L.J.M., S.C.), and the University of British Columbia, Vancouver (J. Christenson, R.S.) — all in Canada; the Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee (T.P.A., R.C.); Dallas–Fort Worth Center for Resuscitation Research, University of Texas Southwestern Medical Center, Dallas (A.H.I., M.I.); and Virginia Commonwealth University Health System, Richmond (J.P.O.).

REFERENCES

1. Berg RA, Hemphill R, Abella BS, et al. Part 5: adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:Suppl 3:S685-705.
2. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA 2005;293:299-304.
3. Christenson J, Andrusiek D, Everson-Stewart S, et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation 2009;120:1241-7.
4. Vaillancourt C, Everson-Stewart S, Christenson J, et al. 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; 82:1501-7.
5. Berg RA, Sanders AB, Kern KB, et al. Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. Circulation 2001;104:2465-70.
6. Kern KB, Hilwig RW, Berg RA, Sanders AB, Ewy GA. Importance of continuous chest compressions during cardiopulmonary resuscitation: improved outcome during a simulated single lay-rescuer scenario. Circulation 2002;105:645-9.
7. Berg RA, Hilwig RW, Kern KB, Ewy GA. "Bystander" chest compressions and assisted ventilation independently improve outcome from piglet asphyxial pulseless "cardiac arrest." Circulation 2000;101: 1743-8.
8. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. JAMA 2010;304:1447-54.
9. Bobrow BJ, Clark LL, Ewy GA, et al. Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. JAMA 2008;299: 1158-65.
10. Brown SP, Wang H, Aufderheide TP, Vaillancourt C, Schmicker RH, Cheskes S, et al. A randomized trial of continuous versus interrupted chest compressions in out-of-hospital cardiac arrest: rationale for and design of the Resuscitation Outcomes Consortium Continuous Chest Compressions Trial. Am Heart J 2015;169(3):334-341.e5.
11. Hostler D, Everson-Stewart S, Rea TD, et al. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: prospective, cluster-randomised trial. BMJ 2011;342:d512.
12. Aufderheide TP, Nichol G, Rea TD, et al. A trial of an impedance threshold device in out-of-hospital cardiac arrest. N Engl J Med 2011;365:798-806.
13. Stiell IG, Nichol G, Leroux BG, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. N Engl J Med 2011;365:787-97.
14. Kudenchuk PJ, Brown SP, Daya M, et al. Resuscitation Outcomes Consortium–Amiodarone, Lidocaine or Placebo Study (ROC-ALPS): rationale and methodology behind an out-of-hospital cardiac arrest antiarrhythmic drug trial. Am Heart J 2014;167(5):653-659.e4.
15. Huber PJ. The behaviour of maximum likelihood estimates under non-standard conditions: Fifth Berkeley Symposium on Mathematical Statistics and Probability. Berkeley: University of California Press, 1967.
16. White HD. Maximum likelihood estimation of misspecified models. Econometrica 1982;50:1-25.
17. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken, NJ: Wiley, 2002.
18. Kellum MJ, Kennedy KW, Ewy GA. Cardiocerebral resuscitation improves survival of patients with out-of-hospital cardiac arrest. Am J Med 2006;119:335-40.
19. Garza AG, Gratton MC, Salomone JA, Lindholm D, McElroy J, Archer R. Improved patient survival using a modified resuscitation protocol for out-of-hospital cardiac arrest. Circulation 2009;119:2597-605.
20. Bobrow BJ, Ewy GA, Clark L, et al. Passive oxygen insufflation is superior to bag-valve-mask ventilation for witnessed ventricular fibrillation out-of-hospital cardiac arrest. Ann Emerg Med 2009;54(5): 656-662.e1.
21. Panchal AR, Bobrow BJ, Spaite DW, et al. Chest compression-only cardiopulmonary resuscitation performed by lay rescuers for adult out-of-hospital cardiac arrest due to non-cardiac aetiologies. Resuscitation 2013;84:435-9.
22. Campbell JP, Maxey VA, Watson WA. Hawthorne effect: implications for prehospital research. Ann Emerg Med 1995; 26:590-4.
23. Link MS, Atkins DL, Passman RS, et al. Part 6: electrical therapies: automated external defibrillators, defibrillation, cardioversion, and pacing: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122:Suppl 3:S706-719.
24. Stub D, Schmicker RH, Anderson ML, et al. Association between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. Resuscitation 2015;92:45-52.
25. Callaway CW, Schmicker RH, Brown SP, et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. Resuscitation 2014;85:657-63.
26. Strote JA, Maynard C, Olsufka M, et al. Comparison of role of early (less than six hours) to later (more than six hours) or no cardiac catheterization after resuscitation from out-of-hospital cardiac arrest. Am J Cardiol 2012;109:451-4.
27. Hollenbeck RD, McPherson JA, Mooney MR, et al. Early cardiac catheterization is associated with improved survival in comatose survivors of cardiac arrest without STEMI. Resuscitation 2014;85:88-95.
28. Agarwal R. The low-flow or high-flow oxygen delivery system and a low-flow or high-flow nonrebreather mask. Am J Respir Crit Care Med 2006;174:1055.
29. Vereczki V, Martin E, Rosenthal RE, Hof PR, Hoffman GE, Fiskum G. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. J Cereb Blood Flow Metab 2006;26:821-35.
30. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-71.
31. Young P, Bailey M, Bellomo R, et al. Hyperoxic Therapy or Normoxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): a randomised controlled feasibility trial. Resuscitation 2014;85:1686-91.
32. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med 2004;32: Suppl:S345-351.