Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial

Tom P Aufderheide, Ralph J Frascone, Marvin A Wayne, Brian D Mahoney, Robert A Swor, Robert M Domeier, Michael L Olinger, Richard G Holcomb, David E Tupper, Demetris Yannopoulos, Keith G Lurie

Summary

Background **Active compression-decompression cardiopulmonary resuscitation (CPR) with decreased intrathoracic pressure in the decompression phase can lead to improved haemodynamics compared with standard CPR. We aimed to assess effectiveness and safety of this intervention on survival with favourable neurological function after out-of-hospital cardiac arrest.**

Methods **In our randomised trial of 46 emergency medical service agencies (serving 2·3 million people) in urban, suburban, and rural areas of the USA, we assessed outcomes for patients with out-of-hospital cardiac arrest according to Utstein guidelines. We provisionally enrolled patients to receive standard CPR or active compression-decompression CPR with augmented negative intrathoracic pressure (via an impedance-threshold device) with a computer-generated block randomisation weekly schedule in a one-to-one ratio. Adults (presumed age or age ≥18 years) who had a non-traumatic arrest of presumed cardiac cause and met initial and final selection criteria received designated CPR and were included in the final analyses. The primary endpoint was survival to hospital discharge with favourable neurological function (modified Rankin scale score of ≤3). All investigators apart from initial rescuers were masked to treatment group assignment. This trial is registered with ClinicalTrials.gov, number NCT00189423.**

Findings **2470 provisionally enrolled patients were randomly allocated to treatment groups. 813 (68%) of 1201 patients assigned to the standard CPR group (controls) and 840 (66%) of 1269 assigned to intervention CPR received designated CPR and were included in the final analyses. 47 (6%) of 813 controls survived to hospital discharge with favourable neurological function compared with 75 (9%) of 840 patients in the intervention group (odds ratio 1·58, 95% CI 1·07–2·36; p=0·019). 74 (9%) of 840 patients survived to 1 year in the intervention group compared with 48 (6%) of 813 controls (p=0·03), with equivalent cognitive skills, disability ratings, and emotional-psychological statuses in both groups. The overall major adverse event rate did not differ between groups, but more patients had pulmonary oedema in the intervention group (94 [11%] of 840) than did controls (62 [7%] of 813; p=0·015).**

Interpretation **On the basis of our findings showing increased effectiveness and generalisability of the study intervention, active compression-decompression CPR with augmentation of negative intrathoracic pressure should be considered as an alternative to standard CPR to increase long-term survival after cardiac arrest.**

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Introduction

More than 800 000 Europeans and North Americans have an out-of-hospital cardiac arrest every year, with overall survival averaging 5%.[1,2] Poor survival rates persist, in part, because manual chest compressions and ventilation, termed standard cardiopulmonary resuscitation (CPR), is inherently inefficient, providing less than 25% of healthy blood flow to the heart and brain.[3] Haemodynamics are often compromised further by poor standard CPR technique, especially inadequate chest compression and incomplete chest recoil.[4–6]

Augmentation of negative intrathoracic pressure during the decompression phase can increase cardiac and cerebral perfusion in animals and people during CPR.[7–12] Investigators have shown that a decrease in intrathoracic pressure is linked to a simultaneous decrease in intracranial pressure; these mechanisms underlie the increase in blood flow to the heart and brain.[7–14] Clinical studies[15,16] have also shown substantial improvement in 24-h survival with this approach. Active compression-decompression CPR increases ventilation to 13·5 L per min (SD 5·5) compared with 7·8 L per min (5·3) with standard CPR.[9,12] One study[17] on the mechanism of the combination of active compression-decompression CPR and an impedance-threshold device showed that active compression-decompression CPR alone did not substantially reduce airway pressures during the decompression phase of CPR, because respiratory gases entered the lungs with every chest decompression. However, the study[17] also showed that when used in

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Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, USA (Prof T P Aufderheide MD); **Department of Emergency Medicine, Regions Hospital, St Paul, MN, USA** (R J Frascone MD); **Whatcom County Emergency Medical Services, Department of Emergency Medicine, Peace Health, St Joseph Medical Center, Bellingham, WA, USA** (M A Wayne MD); **Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN, USA** (B D Mahoney MD, Prof K G Lurie MD); **Department of Emergency Medicine, William Beaumont Hospital, Royal Oak, MI, USA** (Prof R A Swor DO); **Department of Emergency Medicine, St Joseph Mercy Hospital, Ann Arbor, MI, USA** (R M Domeier MD); **Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA** (Prof M L Olinger MD); **Quintiles Consulting, Rockville, MD, USA** (R G Holcomb PhD); **Departments of Neurology and Medicine—Cardiovascular Division, University of Minnesota Medical Center, Minneapolis, MN, USA** (Prof D E Tupper PhD, D Yannopoulos MD, K G Lurie)

Correspondence to:
Prof Tom P Aufderheide, Department of Emergency Medicine, 9200 West Wisconsin Avenue, Pavilion 1P, Milwaukee, WI 53226, USA
taufderh@mcw.edu

combination with an impedance-threshold device to impede inspiratory gases selectively during the recoil phase, active compression-decompression CPR substantially lowered intrathoracic pressures during chest decompression.

The potential effect of augmentation of negative intrathoracic pressure during CPR on long-term survival with good neurological function has not previously been assessed in a clinical trial. We aimed to establish whether active compression-decompression CPR plus a decrease in intrathoracic pressure during the chest recoil phase achieved with an impedance-threshold device would result in improved survival to hospital discharge with favourable neurological function,[18] compared with standard CPR.

Methods

Study design

For the **study protocol** see http://www.advancedcirculatory.com/RESQTrial-IP.pdf

We undertook our randomised, multicentre trial in seven geographical sites in the USA: Minneapolis and St Paul (MN), Whatcom County (WA), Oshkosh (WI), Oakland and Macomb Counties and Washtenaw and Livingston Counties (MI), and Indianapolis (IN). These sites had 46 emergency medical service agencies in urban, suburban, and rural areas, and served 2·3 million people.

Adults (presumed or known to be ≥18 years of age) with out-of-hospital cardiac arrest were eligible for the study, on the basis of local institutional review board requirements. Patients were initially excluded if the patient was presumed or known to be younger than 18 years of age; had obvious or likely traumatic injuries causing cardiac arrest, a pre-existing do-not-resucitate order, signs of obvious clinical death, conditions that precluded the use of CPR, an in-hospital cardiac arrest, recent sternotomy with wound not appearing completely healed (if unknown) or less than 6 months (if known); or if the family or legal guardians requested that they not be entered in the study at the time of arrest. The final exclusion criteria included all initial criteria and if the patient received less than 1 min of CPR by emergency medical service personnel; had a complete airway obstruction that could not be cleared or if attempts at advanced airway management were unsuccessful; intubation with a leaky or uncuffed advanced airway device; or a stoma, tracheotomy, or tracheostomy. We excluded patients with non-cardiac causes of arrest, including respiratory arrest (eg, pulmonary embolism), arrest due to haemorrhage causes or stroke, metabolic abnormalities (eg, hyperkalaemia), drug overdose, and electrocution, to meet Utstein[19] cardiac arrest criteria for our prespecified primary endpoint analyses.

The study was approved by the US Food and Drug Administration (FDA) under the US Code of Federal Regulations (21 CFR 50.24) exemption from informed consent under emergency circumstances, which included community consultation and public notification. Patient or family members provided written informed consent for continued participation in the trial before neurological assessment. The protocol was undertaken with an investigational device exemption (IDE #G050062) and approved by the FDA and 25 institutional review boards at hospitals to which study patients were likely to have been transported.

Randomisation and masking

We used a prospective computer-generated block randomisation schedule every week, in blocks of 4 weeks, which was prepared by an independent biostatistician (RGH), to assign patients to receive standard CPR or study intervention in a one to one ratio. Apart from rescuer CPR, all aspects of the study, including obtaining of patient consent, medical record review, and neurological assessments, were done masked to treatment assignment, including during systematic review of hospital charts for adverse events. Study coordinators provided patient information and follow-up assessment documents that did not show treatment assignment to study nurses (who obtained patient consent and did the neurological assessments) at every site. Hospital personnel who were responsible for post-resuscitation care were masked to the CPR method to the extent possible. The study sponsor was masked to all aggregate patient outcomes throughout the study, apart from device failures.

An independent data and safety monitoring board monitored safety, ethical, and scientific aspects of the study. An independent clinical events committee was responsible for adjudication of individual patient's adverse events and for exclusion of all those screened who did not meet criteria for enrolment, or did not meet the final selection criteria. With the unavoidable exception of device failures, patient information provided in summary form to the clinical events committee did not show randomised assignment. The data and safety monitoring board was masked to study group assignment when rendering recommendations to the investigators.

Procedures

Rescuers did active compression-decompression CPR with a hand-held device consisting of a suction cup that was attached to the chest, a handle, an audible metronome set to 80 beats per minute, and a force gauge to guide compression depth and chest wall recoil.[15,16] This CPR technique requires the operator to compress to the same depth as standard CPR and then lift upward to fully decompress the chest.[15,16] An impedance-threshold device, with an inspiratory resistance of 16 cm H_2O and less than 5 cm H_2O expiratory impedance, was connected to a facemask or advanced airway. The impedance threshold device lowered intrathoracic pressure during the decompression phase by impeding passive inspiratory gas exchange during the chest recoil phase, yet allowing periodic positive pressure ventilation.[10,17] The CPR device (ResQPump, also called CardioPump) and

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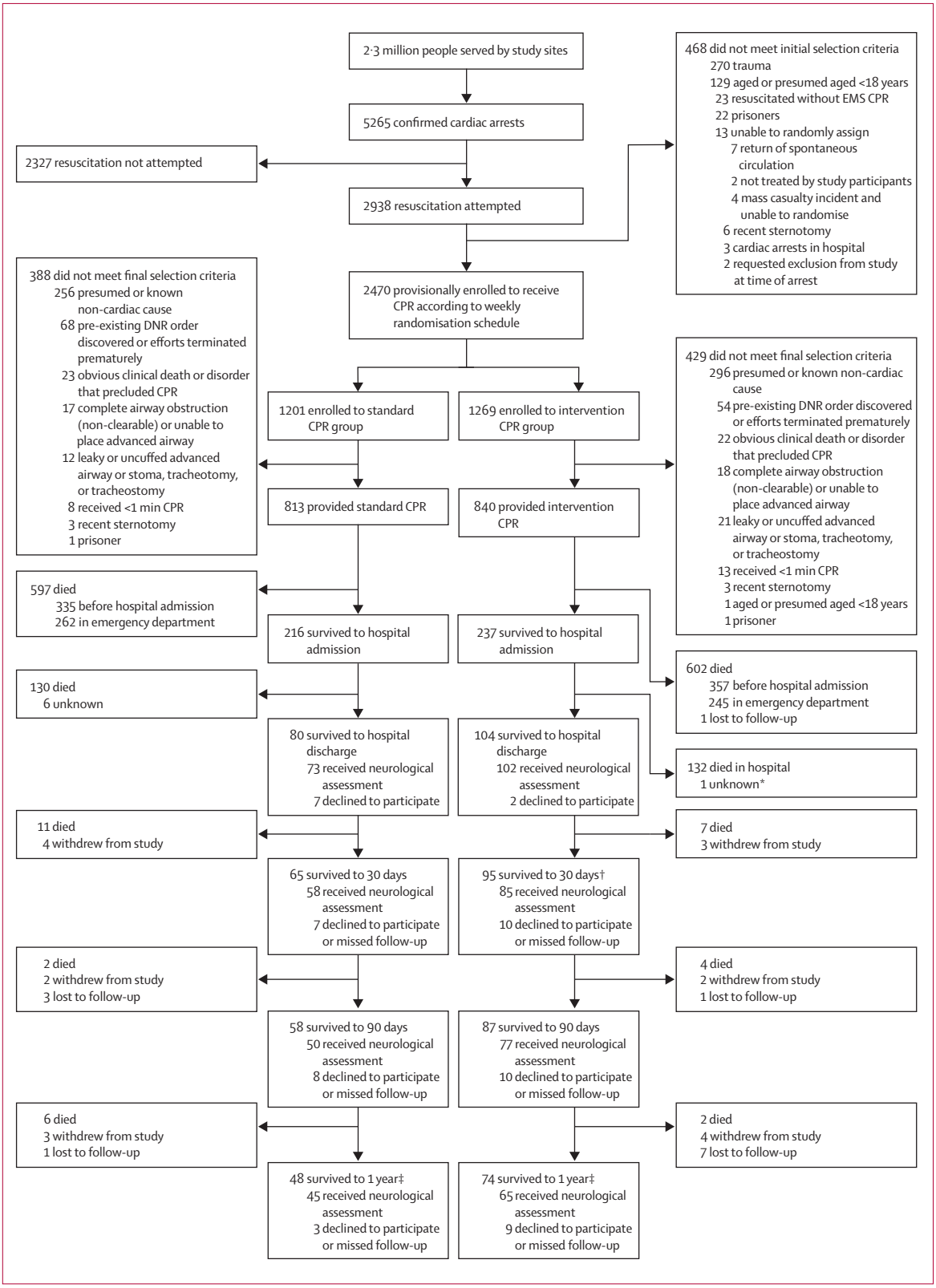

Figure 1: **Study profile**
Our study was carried out in line with the Utstein guidelines.[19] DNR=do not resuscitate. EMS=emergency medical services. CPR=cardiopulmonary resuscitation. Traditional resuscitation was provided in the standard CPR group. *Patient was confirmed dead by public records. The date of death was before 30 days after cardiac arrest, but whether the death occurred during the index hospital stay is unknown. †One patient survived to day 30 and underwent neurological assessment, but had not been discharged from hospital. ‡We searched public death records at 1 year for all patients who withdrew or were lost to follow-up at any stage.

	Standard CPR group (n=813)	Intervention* group (n=840)
Mean age (years)	66·8 (14·5)	67·0 (15·2)
18–34	12 (2%)	11 (1%)
35–44	36 (4%)	47 (6%)
45–54	114 (14%)	133 (16%)
55–64	215 (26%)	179 (21%)
65–74	172 (21%)	169 (20%)
75–84	162 (20%)	192 (23%)
≥85	102 (13%)	109 (13%)
Sex (male)	539 (66%)	558 (66%)
Arrest surroundings		
Witnessed before arrival of first responder	383 (47%)	398 (47%)
Witnessed after arrival of first responder	76 (9%)	80 (10%)
Unwitnessed	353 (43%)	361 (43%)
Data not available	1 (<1%)	1 (<1%)
Bystander CPR		
Provided	350 (43%)	357 (43%)
Data not available	1 (<1%)	..
Initial recorded cardiac arrest rhythm		
Ventricular fibrillation and pulseless ventricular tachycardia	247 (30%)	292 (35%)
Asystole	379 (47%)	375 (45%)
Pulseless electrical activity	180 (22%)	170 (20%)
Data not available	7 (<1%)	3 (<1%)
Emergency call to first response time (min)	6·5 (3·3)	6·4 (3·1)
Emergency call to EMS CPR start time (min)†	6·6 (3·4)	6·7 (3·2)
Emergency call to placement of study devices† (min)	..	7·1 (3·5)
Impedance-threshold device airway attachment site		
Facemask	..	717 (85%)
Endotracheal tube	..	586 (70%)
Supraglottic airway (eg, laryngeal mask airway, Combitube, King)	..	169 (20%)
Epinephrine dose (mg)	3·3 (2·1)	3·3 (2·1)
Patients without ROSC	3·8 (1·9)	3·8 (1·9)
Duration of CPR (min)	27·6 (12·2)	28·1 (11·4)
Patients without ROSC	32·3 (9·5)	32·3 (8·1)
ROSC during CPR before hospital admission	324 (40%)	343 (41%)
Enrolment site		
1	122 (15%)	121 (14%)
2	155 (19%)	169 (20%)
3	113 (14%)	92 (11%)
4	189 (23%)	208 (25%)
5	46 (6%)	40 (5%)
6	149 (18%)	169 (20%)
7	39 (5%)	41 (5%)
Admitted to hospital	216 (27%)	237 (28%)
In-hospital hypothermia (% admitted)	85 (39%)	92 (39%)
Cardiac catheterisation (% admitted)	72 (33%)	100 (42%)
Coronary stenting (% admitted)	28 (13%)	38 (16%)
Coronary bypass surgery (% admitted)	6 (3%)	15 (6%)
Implanted cardiodefibrillator (% admitted)	30 (14%)	41 (17%)

Data are number (%) or mean (SD) unless otherwise stated, and include all patients who met final study enrolment endpoint criteria. CPR=cardiopulmonary resuscitation. EMS=emergency medical service. ROSC=return of spontaneous circulation. *Patients received active compression-decompression cardiopulmonary resuscitation plus an impedance-threshold device. †Data do not include arrests witnessed by EMS personnel.

Table 1: **Baseline patient characteristics**

the impedance-threshold device (ResQPOD) were manufactured by Advanced Circulatory Systems (Roseville, MN, USA).

The first basic or advanced life support emergency medical service provider to arrive started chest compressions as soon as possible for both study groups. Standard CPR, defibrillation, and advanced life support treatment were done in accordance with local policy and the American Heart Association guidelines.[20] The compression to ventilation ratio was 30 to 2 during basic life support for both CPR techniques. For the intervention protocol, rescuers provided CPR at 80 compressions per min as soon as possible, with the active compression-decompression CPR device force gauge used to help achieve the recommended compression depth and complete chest recoil. For this group, rescuers initially attached the impedance-threshold device between the ventilation bag and facemask (King Systems, Indianapolis, IN, USA) and the device was subsequently relocated to the advanced airway. The impedance-threshold device was removed if the patient had return of spontaneous circulation and reapplied if rearrest occurred. The devices and facemask for the study intervention group (or a facemask alone for the standard CPR group) were packaged together in a study bag and carried by rescue personnel as per the randomisation calendar. CPR efforts in both groups were encouraged for at least 30 min on scene before the resuscitation attempt was stopped. Study intervention, if in progress, was stopped on arrival to hospital and replaced with traditional CPR, if warranted. In-hospital therapeutic hypothermia and cardiac revascularisation for all patients were encouraged by all site investigators.[20]

4940 emergency medical service personnel underwent didactic and hands-on training before the study started and every 6 months thereafter. Comprehensive training in standard CPR and the study intervention was provided by the principal investigators and research team at each study site, and emphasised the need to start compressions immediately; provide adequate compression depth, rate, and full chest recoil; maximise hands-on time, appropriate ventilation rate, and duration; ensure appropriate facemask seal for impedance-threshold device use with a facemask (two-handed technique);[20] do active compression-decompression CPR;[21,22] and rotate personnel undertaking CPR every 2 min to avoid fatigue.[20–22]

Endpoints

The prespecified primary study endpoint was survival to hospital discharge with favourable neurological function, defined as a modified Rankin scale score of 3 or less.[18] This neurological assessment took into account previous neurological deficits and was undertaken at the time of hospital discharge. A secondary safety endpoint assessed the rate of major adverse events until hospital discharge.

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Major adverse events that occurred during the resuscitative effort or subsequent hospital stay that we included in the assessment of secondary safety endpoint were death, cerebral bleeding, bleeding requiring transfusion or requiring surgical intervention, seizures, rearrest, pulmonary oedema, chest fractures (rib or sternum), internal thoracic and abdominal injuries, and device malfunction or defects.

To discern if the study intervention resulted in more patients with neurological impairment (ie, modified Rankin scale ≥4), we assessed additional secondary effectiveness endpoints at 90 days and 365 days after out-of-hospital cardiac arrest. We assessed attention, short-term and long-term memory, judgment, and spatial ability with the cognitive abilities screening instrument.[23] We established amount of functional disability with the disability rating index[24] and depression and emotional stability with the Beck depression inventory.[25]

Adverse events

We regarded all adverse events reported as major because of their nature and the working understanding that only serious events associated with CPR interventions would be recorded. If a patient died and was not transported to hospital, the only major adverse event assigned to that patient was death. Post-mortems were not routinely reported and a uniform assessment of other adverse events before hospital admission was not possible. However, all patients who were transported to hospital had all reported adverse events before hospital discharge included in calculation of the event rates, including those that occurred before transport to hospital. Events of an equivalent nature were combined for reporting reasons by use of protocol-defined major adverse events. For example, rib, sternal, and spinal fractures were all coded as chest fractures. Chest organ injury and abdominal organ injury were coded as internal organ injury. Adverse events identified as other were individually examined and included in protocol-defined adverse-event groups, if possible. For example, pneumomediastinum was coded into pneumothorax. Adverse events described as fluid in the endotracheal tube or airway were coded as evidence of pulmonary oedema. With only a few exceptions, patients were reported to have only one incident of a particular adverse-event type. In exceptional cases (eg, more than one chest fracture or rearrests) only one event of that type was assigned to an individual patient. Reported rates for individual major adverse event types were based on the percentage of all patients at risk who reported a specific event type.

Data collection

We obtained out-of-hospital data according to Utstein guidelines[19] from the emergency medical service out-of-hospital medical record. We obtained data for in-hospital treatment, outcomes, and follow-up from hospital records and neurological assessment surveys for all patients who

	Standard CPR group (n=813)	Intervention* group (n=840)	p value
Primary composite study endpoints			
Modified Rankin scale score at hospital discharge†			0·039
0	3 (<1%)	11 (1%)	..
1	8 (1%)	11 (1%)	..
2	26 (3%)	30 (4%)	..
3	10 (1%)	23 (3%)	..
4	10 (1%)	9 (1%)	..
5	16 (2%)	18 (2%)	..
6	727 (89%)	734 (87%)	..
Survival data for hospital discharge not available	6 (<1%)	2 (<1%)	..
Survived, but data for MRS not available	7 (<1%)	2 (<1%)	..
MRS ≤3 (primary study endpoint)	47 (6%)	75 (9%)	0·019
Secondary survival endpoints			
Survived to 24 h after arrest	176 (22%)	197 (24%)	0·41
Data not available	9 (1%)	6 (<1%)	..
Survived to hospital discharge	80 (10%)	104 (12%)	0·12
Data not available	6 (<1%)	2 (<1%)	..
Discharge location (% discharged)			
Home	47 (59%)	67 (64%)	0·75
Other	28 (35%)	35 (34%)	..
Data not available	5 (6%)	2 (2%)	..
Survived to 90 days	58 (7%)	87 (10%)	0·029
Data not available	15 (2%)	8 (1%)	..
Survived to 1 year	48 (6%)	74 (9%)	0·030
Data not available	19 (2%)	19 (2%)	..
Initial recorded arrest rhythm in patients with MRS ≤3			
Ventricular fibrillation and pulseless ventricular tachycardia	40 (17%)	66 (23%)	0·0645‡
Asystole	3 (<1%)	6 (2%)	..
Pulseless electrical activity	3 (2%)	2 (1%)	..
Unknown	1 (<1%)	1 (<1%)	..
Neurological assessment			
CASI§ (patients with complete score, validity=1)			
90 days	93·2 (7·4)	90·4 (13·4)	0·251
Data not available	19 (33%)	35 (40%)	..
365 days	92·9 (12·0)	94·5 (4·5)	0·473
Data not available	16 (33%)	32 (43%)	..
Beck depression inventory score¶			
90 days	4·8 (3·9)	6·5 (6·8)	0·098
Data not available	14 (24%)	22 (25%)	..
365 days	5·2 (6·3)	5·5 (5·9)	0·862
Data not available	13 (27%)	17 (23%)	..

Data are number (%) or mean (SD) unless otherwise stated, and include all patients who met final study enrolment endpoint criteria. *Patients received active compression-decompression cardiopulmonary resuscitation plus an impedance-threshold device. †For MRS scores, 0 is asymptomatic, 1 is no significant disability, 2 is slight disability, 3 is moderate disability, 4 is moderately severe disability, 5 is severe disability, and 6 is dead. ‡Mantel-Haenszel test statistic across three initial recorded arrest rhythm groups. §Assessment of attention, short-term memory, long-term memory, judgment, spatial ability, concentration, based on a scale of 0–100, in which 100 is a perfect score. ¶Assessment of depression with a scale of 0–63, in which 0–13 suggests minimum signs of depression, 14–19 suggests mild signs of depression, 20–28 suggests moderate signs of depression, and 29–63 suggests severe signs of depression. MRS=modified Rankin scale. CASI=cognitive abilities screening instrument.

Table 2: **Primary and secondary study endpoints**

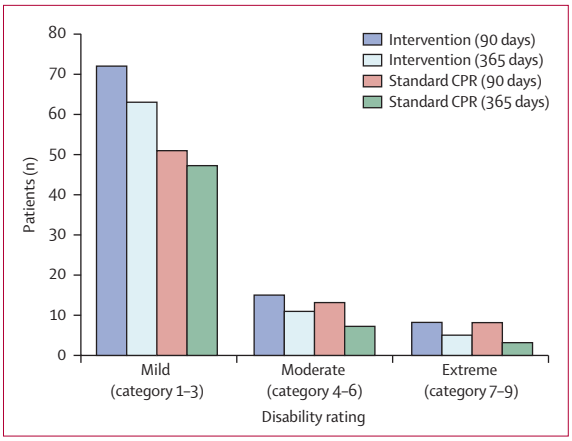

Figure 2: **Disability rating scale scores 90 days and 365 days after out-of-hospital cardiac arrest**

Scores did not differ between study groups at 90 days and 365 days after cardiac arrest. The disabilities rating scale[23] is based on a scale of 0–29 where disability is absent (score 1, category 1), mild (1, 2), partial (2–3, 3), moderate (4–6, 4), moderately severe (7–11, 5), severe (12–16, 6), extremely severe (17–21, 7), vegetative state (22–24, 8), or extreme vegetative state (25–29, 9). CPR=cardiopulmonary resuscitation.

consented to be included or until such time as the patient or family refused consent for continued participation in the trial. All neurological assessments were done by trained and certified nurses who were members of the research team at every study site.

We undertook clinical monitoring throughout the study to maximise protocol adherence and quality of rescuer performance of standard CPR and the study intervention. Study sites were required to complete a run-in phase and certification process before beginning enrolment in the study.

Statistical analysis

On the basis of historical controls in equivalent populations at participating study sites, we estimated that survival to hospital discharge in the control group would be about 6%. Estimates of survival to hospital discharge with a good neurological outcome based on the modified Rankin scale score had not previously been assessed in this population. On the basis of an expected 6% rate in the standard CPR control group for the study endpoint and 10·2% in the intervention group, a sample size of 700 patients per group would have been needed to detect a significant improvement with a final significance level of 0·049 with 80% statistical power. An interim analysis at the 50% information point of the original study sample was prospectively planned with the Lan-DeMets alpha spending method with O'Brien-Fleming boundaries.[26] Following this planned midpoint analysis in September, 2008, the data and safety monitoring board recommended a sample size adjustment to 2696 assessable patients (1348 per group) to maintain the original design objective of 80% power to detect a group difference, without knowledge of the direction of the recorded difference. In July, 2009, the study was stopped early because of a shortage of funding, at which time 1653 patients who met final criteria had been enrolled. At study end, we applied the original prespecified criteria for assessment of statistical significance of study results, which was identical to requirements that would have been applicable to full enrolment.

Our original study design initially included a third group of patients who were randomly assigned to standard CPR and an impedance-threshold device. The trial was originally designed to primarily compare standard CPR with active compression-decompression CPR and an impedance-threshold device. The third group was added (with half the proportional enrolment of the other two groups assigned initially to the third arm) to assess the relative contribution of the impedance-threshold device alone to anticipated treatment effect observed for the combination of devices. Although masked to outcome by study group, this group was discontinued in November, 2007, after enrolment of 150 patients because of slower than expected overall enrolment and our intention to funnel remaining funding resources to assessment of the primary outcome. Patients from the third group are not included in analyses presented here.

We used Fisher's exact test for analysis of the primary endpoint and $p<0·049$ was regarded as statistically significant. We did all analyses on the intention-to-treat population of all patients meeting enrolment criteria. We assessed the secondary safety endpoint with an exact binomial test for non-inferiority with the same p-value requirement. We compared proportions of patients who had one or more major adverse events (of any kind) between study groups, and tested whether the patient-scale major adverse event rate in the intervention group was inferior or non-inferior to that of the control group with a non-inferiority margin of 5%. We assessed additional prespecified secondary endpoints, including subgroup analyses based upon age, sex, initial rhythm, time to CPR, and whether the arrests were witnessed, with Fisher's exact tests and Student's *t* tests, but associated p-values were regarded as nominal and unadjusted without associated statistical significance values. We did all analyses with StatXact version 8 and SPSS version 18.0. Continuous data are expressed as mean (SD).

This trial is registered with ClinicalTrials.gov, number NCT00189423.

Role of the funding source

The protocol was approved by the US National Institutes of Health (funding source) and a representative of this institute was on the data and safety monitoring board. The sponsor (Advanced Circulatory Systems) helped investigators to obtain government funding, design the study, interpret the data, write the report, and decide to

submit the report for publication. The sponsor was not involved in any patient care or assessment of patient neurological status during the 1-year follow-up. The decision to submit the paper was made by all co-authors with no input from the National Institutes of Health. The corresponding author had full access to all the data in the study; all other authors could request examination of any of the data elements. All authors reviewed and approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Results

We enrolled a total of 197 patients in a run-in phase across all sites, starting in October, 2005, at the first site, and ending in April, 2009, at the last participating site. Data from the run-in phase were not included in the final analyses. The mean run-in period across the seven sites was 107 days (range 21 to 173 days). Between March, 2006, and July, 2009, we randomly assigned 2470 patients to treatment groups, 1653 of whom met prespecified enrolment criteria (figure 1). We completed the final 1-year follow-up in July, 2010. Enrolment was balanced between study groups across all sites (table 1). The site with the lowest enrolment rate enrolled 80 patients (site 7; 4·8% of patients in the study population) and highest enrolled 397 (site 4; 24·0%). For 672 (80%) patients, the impedance-threshold device was used first with a facemask and then switched to an advanced airway. The impedance-threshold device was used only on a facemask in 45 (5·4%) cases and an advanced airway was only used in 73 (8·5%). The impedance-threshold device was not used in 50 cases (5·9%).

For the primary endpoint, treatment with study intervention led to a 53% relative increase in survival to hospital discharge with a modified Rankin scale score of 3 or less compared with standard CPR (odds ratio 1·58, 95% CI 1·07–2·36, p=0·019; table 2). Additionally, there was a shift in the distribution of modified Rankin scale scores in favour of improved outcomes in the intervention group (Kruskal-Wallis test for ordinal responses p=0·039; table 2).

Our subgroup analysis of survival based on the first recorded rhythm to hospital discharge with a modified Rankin scale score of 3 or less suggested survival did not differ between patients with ventricular fibrillation and pulseless ventricular tachycardia in the intervention group and those in the standard CPR group (p=0·0645, table 2). 74 of 218 (34%) patients with ventricular fibrillation and pulseless ventricular tachycardia who had a witnessed out-of-hospital cardiac arrest in the intervention group survived to hospital discharge, compared with 50 of 181 (27%) such patients in the standard CPR group (p=0·19).

Nearly all survivors had no or mild long-term neurological deficits, which did not differ between groups (table 2). Disabilities rating scale scores, which are a key functional assessment of patients with severe disability, did not differ between groups (figure 2). Overall major adverse event rates did not differ between groups (table 3).

	Standard CPR group (n=813)	Intervention* group (n=840)	p value
Patients with reported adverse events†			0·681
≥1	766 (94%)	787 (94%)	
0	47 (6%)	53 (6%)	
Adverse events			
Death	729 (90%)	734 (87%)	0·165
Rearrest	161 (20%)	184 (22%)	0·304
Pulmonary oedema‡	62 (8%)	94 (11%)	0·015
Seizure after index arrest	13 (2%)	11 (1%)	0·683
Bleeding requiring transfusion or surgery	3 (<1%)	7 (<1%)	0·343
Chest fractures	15 (2%)	12 (1%)	0·563
Pneumothorax	7 (<1%)	10 (1%)	0·628
Haemothorax	1 (<1%)	2 (<1%)	1·000
Cardiac tamponade	3 (<1%)	2 (<1%)	0·682
Cerebral bleeding	3 (<1%)	2 (<1%)	0·682
Aspiration	7 (<1%)	8 (1%)	1·000
Internal organ injury	2 (<1%)	4 (<1%)	0·687
Other	3 (<1%)	1 (<1%)	0·367
Study device functionality			
Impedance-threshold device			
Timing light failure	NA	59 (7%)§	..
ACD-CPR device			
Inadequate attachment of suction cup to the chest	NA	81 (9%)¶	..

Data are number (%) or mean (SD), and include all patients who met final study enrolment endpoint criteria. CPR=cardiopulmonary resuscitation. ACD=active compression-decompression. NA=not applicable. *Patients received ACD cardiopulmonary resuscitation plus an impedance-threshold device. †p<0·0001 for non-inferiority within a margin of 5%. ‡Pulmonary oedema included prehospital reports of any fluid or secretions noted in the airway (eg, oedema fluid, blood, or mucus) and pulmonary oedema or pulmonary/pleural effusion that was reported on radiography or CT imaging. §The impedance-threshold device timing light is an accessory feature to guide ventilation rate. Primary function of the impedance-threshold device was not affected by timing light failures in any cases as the device provided appropriate inspiratory impedance. Manufacturing changes have been implemented to remedy timing light failures. ¶For 73 of 81 (90%) reported cases of difficulty maintaining suction, use of the ACD-CPR device was continued despite suction cup attachment difficulty. For eight (10%) of these 81 patients, use of the ACD-CPR device was discontinued and replaced with manual standard CPR.

Table 3: **Major adverse events and device functionality**

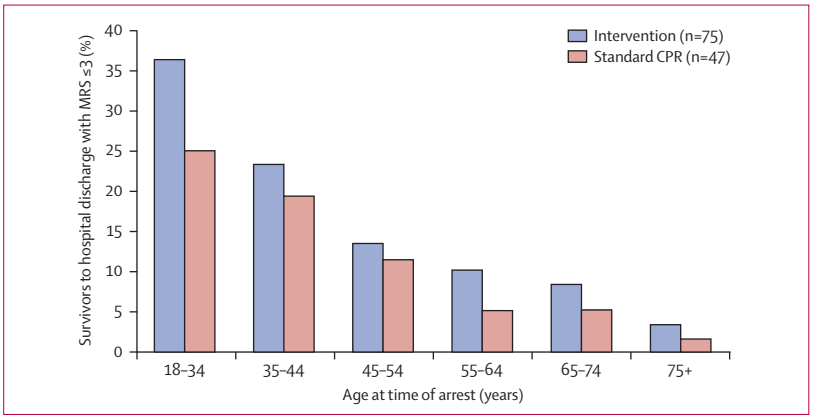

Figure 3: **Age of patients surviving to hospital discharge with favourable neurological function (MRS score ≤3)**
CPR=cardiopulmonary resuscitation. MRS=modified Rankin scale.[18]

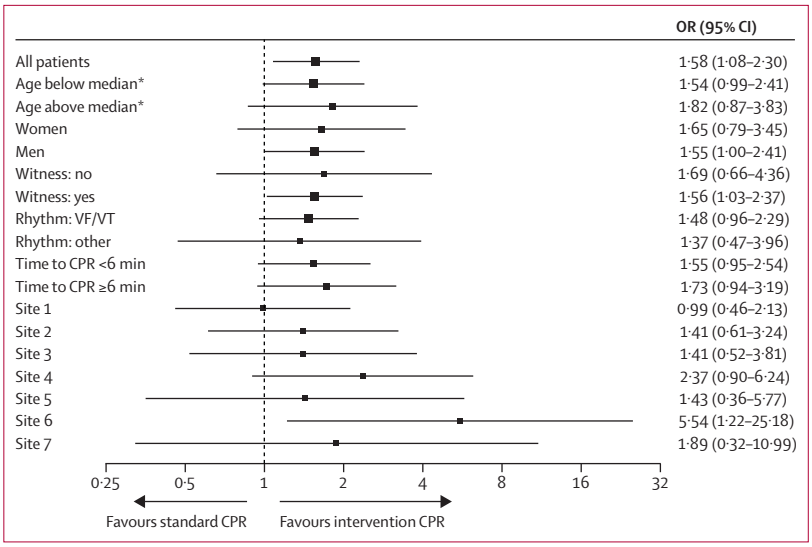

Figure 4: **Effects of age, study site, sex, and treatment intervention on primary study endpoint**
Estimated odds ratios exceeded 1·00 for subgroups based on age, sex, witnessed status, time to start of CPR, and all study sites apart from Site 1. VF/VT=ventricular fibrillation and pulseless ventricular tachycardia. CPR=cardiopulmonary resuscitation. *Median age was 67 years (IQR 56–79).

However, pulmonary oedema was more common in the intervention group (p=0·015).

We assessed the effects of age, study site, sex, and date of treatment on the primary endpoint. The average age of survivors at this endpoint was 56·0 years (SD 15·0) in the standard CPR group and 56·4 years (15·4) in the study intervention group (p=0·87). Figure 3 shows age distributions of patients surviving to the primary endpoint. Consistent survival differences between study groups were noted throughout the study, independent of age, study site, sex, and date of treatment (figures 4 and 5). In the standard CPR group, 12 (4%) of 274 women and 35 (6%) of 539 men survived to the primary endpoint compared with 20 (7%) of 282 women and 55 (10%) of 558 men in the intervention group. Furthermore, the therapeutic benefit of CPR in both groups was highly dependent on time to the start of CPR (figure 6). There were no survivors with favourable neurological function in either group when professional rescuer CPR was started more than 10 min after the emergency call.

We excluded 817 patients from the primary analysis who did not meet prespecified enrolment criteria (eg, non-cardiac causes or inability to ventilate). When data from these patients were combined with those meeting prespecified enrolment criteria, 71 (6%) of 1201 treated with standard CPR survived to the primary endpoint compared with 101 (8%) of 1269 in the intervention group (odds ratio 1·37, 95% CI 0·99–1·90; p=0·057).

Primary endpoint data were missing for 17 patients who survived to hospital admission, and informed consent for study participation was refused by 14 patients or family members. We also did a sensitivity analysis to establish the effect of missing cases, assuming patients who were known to be dead within 1 year from public death records or those known to be discharged to a nursing home probably had a modified Rankin scale score of more than 3 at hospital discharge. In our sensitivity analysis, assessing the effect of missing data, the difference between the standard CPR and intervention groups remained significant (p=0·018).

See Online for webappendix

Webappendix pp 1–4 contains supplementary tables with data for patients in whom resuscitation was not attempted due to clinical death or do-not-resuscitate orders; initial selection criteria were not met; exclusions were made for non-cardiac causes; modified Rankin scale score information was missing; and who were alive at hospital discharge and subsequently died, withdrew from the study, or were lost to follow up.

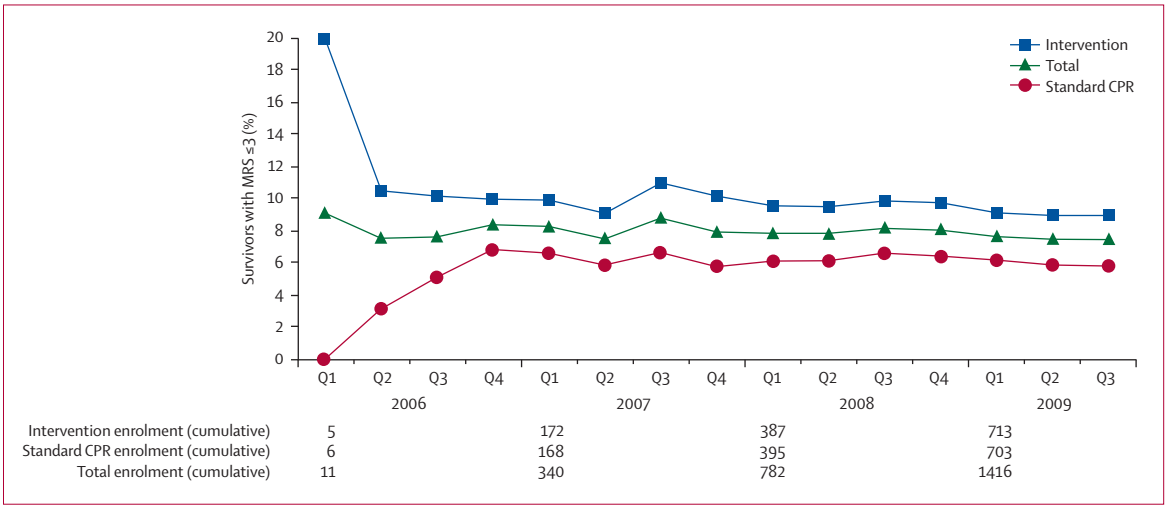

Figure 5: **Cumulative rates of achievement of primary endpoint (MRS score ≤3 at discharge from hospital)**
Results are shown for pivotal phase enrolment (n=1653) by year quarter (Q). Consistent results in both groups were shown throughout the whole study. Enrolment was initiated in the fourth quarter of 2007 in Site 6 and the first quarter of 2009 in Site 7. MRS=modified Rankin scale. CPR=cardiopulmonary resuscitation.

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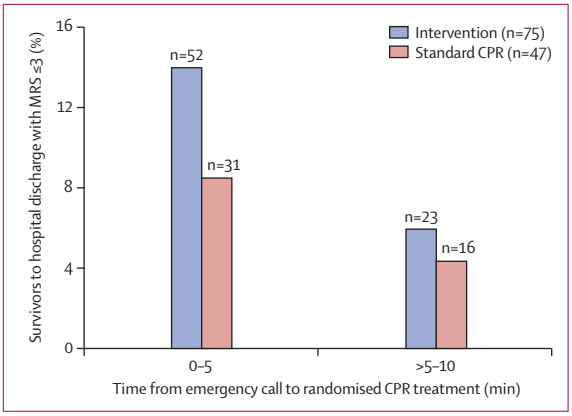

Figure 6: **Survival at hospital discharge with favourable neurological function (MRS score ≤3 at discharge from hospital) by time to CPR treatment**
Survival at hospital discharge with MRS ≤3 was significantly higher in the intervention group than in the standard CPR group (odds ratio 1·58, 95% CI 1·07–2·36, p=0·019). There were no survivors with favourable neurological function in either group if CPR was initiated more than 10 min after the emergency call. MRS=modified Rankin scale. CPR=cardiopulmonary resuscitation.

Discussion

Our results show that treatment with active compression-decompression CPR with enhancement of negative intrathoracic pressure during the decompression phase significantly increases survival to hospital discharge with favourable neurological function compared with standard CPR after an out-of-hospital cardiac arrest of presumed cardiac cause (panel). Furthermore, overall survival increased by nearly 50% by 1 year in the intervention group compared with controls. Consistency of benefit was independent of sex, age, date of enrolment, and study site. Neurological function was much the same between groups at 90 days and 365 days after the out-of-hospital cardiac arrest.

There was no increase in the number of patients with severe neurological impairment in either group. There were no differences in overall major adverse event rates between groups, although occurrence of pulmonary oedema was increased by 50% in the device group, which was coexistent with the increase in survival with favourable neurological function. The clinical relevance of this finding is unclear: the percentage increase in pulmonary oedema (46%) was proportional to the increase in survival in the intervention group (53%). Our findings strongly support the need for rapid deployment of all CPR interventions to maximise possible benefits.

Our investigation builds on previous studies[7–12,15,16,27–31] showing that active compression-decompression CPR and a means to lower intrathoracic pressure during the chest recoil phase transforms the chest into an active bellows to more effectively circulate blood during CPR to the heart and the brain and increase short-term survival. Our study shows that teaching and implementation of active compression-decompression CPR and impedance-threshold device skills in urban, suburban, and rural emergency medical services is practicable. Because the US study sites we investigated have much the same practices as do most emergency medical service systems in the USA and because study devices have been successfully integrated into emergency services at locations in Germany and France, this approach should be expandable to any emergency medical service system that follows present European Resuscitation Council or American Heart Association guidelines.

We first noted the significant difference in clinical outcomes between intervention groups at the time of hospital discharge; return of spontaneous circulation and hospital admission rates did not differ between groups. On the basis of preclinical and clinical studies showing

Panel: Research in context

Systematic review

Investigators have shown the physiological changes underlying the synergistic effects of a combination of active compression-decompression cardiopulmonary resuscitation (CPR) with an impedance threshold device. Active compression-decompression CPR by itself transforms the human chest into an active bellows—ventilation was increased to 13·5 L per min (SD 5·5) compared with 7·8 L per min (5·3) for standard CPR.[9] In that investigation,[9] intrathoracic pressures remained much the same with standard CPR and active compression-decompression CPR unless the endotracheal tube was blocked, thereby preventing respiratory gases from entering the lungs during the chest decompression phase. The mechanical and physiological advantages associated with a lowering of intrathoracic pressure by impedance of inspiration (apart from when active positive pressure ventilation was provided) have been confirmed in various studies of animals and people. Impedance of inspiration lowered intrathoracic pressure and resulted in increased cardiac output, vital organ blood flow, and survival in animals and human patients.[7,10–12,14–17,27–30] Four clinical trials,[15–17,29] including 644 patients, and a meta-analysis[30] done before our clinical investigation provided strong support for the notion that active compression-decompression CPR with augmentation of negative intrathoracic pressure improves haemodynamics, short-term survival, and the potential for longer-term survival with favourable neurological function.

Interpretation

On the basis of the strong clinical foundation we noted, we provide evidence from a study of 1653 patients that active compression-decompression CPR with augmentation of negative intrathoracic pressure improves survival to hospital discharge with favourable neurological function compared with standard CPR. For the first time, we have shown that a new method of CPR increases hospital-discharge rates and 1-year survival, which are both associated with good neurological outcomes, by nearly 50%, compared with the current standard of care, closed-chest manual CPR.

greater blood flow to the heart and brain with active compression-decompression CPR and augmentation of lower intrathoracic pressure,[7,10–12,14,27–29] we suggest that improved cerebral perfusion during CPR in the intervention group resulted in reduced cerebral ischaemia but that recovery and restoration of brain function might take more time than does the recovery of cardiac function. These findings also support the idea that improved perfusion outside the hospital in the intervention group could result in more stable candidates for cardiac catheterisation than were found in the standard CPR group, resulting in more patients in the intervention group being provided cardiac catheterisation.

Our study has several limitations. First, emergency medical service rescuers were not blinded to the CPR method; however, assessors of the primary outcome and neurological tests were masked to intervention status, which restricted potential bias. Second, we could not establish the relative contribution of active compression-decompression CPR alone, the impedance-threshold device alone, or the rescuer feedback elements including the timing lights, metronome, and force gauge to the positive study outcome. Data from studies in animals and human beings suggest that every component is necessary to record benefits with this combined approach.[5,6,11,14,16,30] The study initially included a third arm—standard CPR plus an impedance-threshold device study arm—to assess the relative contribution of the impedance threshold device only to the anticipated benefit of the combination of active compression-decompression CPR plus an impedance-threshold device versus standard CPR. However, due to slower than anticipated enrolment rates for the entire study and limited funding for the study, enrolment in this third study arm was discontinued early in the course of the study. Another potential limitation of our study was that study enrolment was stopped early because of low funding and extra data could have changed the primary findings. Nevertheless, differences between treatment groups were consistent throughout the study (figure 5). Finally, some surviving patients refused to provide consent for further participation or release of data. However, because of the unique circumstances and limitations associated with obtaining of informed consent under emergency circumstances, collection of follow-up data for all patients is a challenge for all studies such as ours.

Thus, compared with standard CPR, active compression-decompression CPR with augmentation of negative intrathoracic pressure results in significantly increased survival to hospital discharge with favourable neurological function, which was observed to 1 year after out-of-hospital cardiac arrest.

Contributors

TPA, RGH, DET, DY, and KGL designed the study. TPA, RJF, MAW, BDM, RAS, RMD, and MLO obtained the data. RGH did the statistical analysis. All authors participated in the data analysis and interpretation processes and in the review of the final report.

Study personnel

Data and Safety Monitoring Board—L Brent Mitchell (Chairman; Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, AB, Canada), Dianne M Bartels and Patricia Grambsch (University of Minnesota, Minneapolis, MN, USA), Daniel Hankins (Mayo Clinic Medical Transport, Rochester, MN, USA), James Malec (Rehabilitation Hospital of Indiana/Indiana University School of Medicine, Indianapolis, IN, USA), Jay W Mason (University of Utah, Salt Lake City, UT, USA), and Paul Molinari (Twin Cities Anesthesia Associates, Minneapolis, MN, USA). *Clinical Events Committee*—Carson Harris (Chairman), Avi Nahum, and Dennis Zhu (Regions Hospital, St Paul, MN, USA). *Data Co-ordination*—Terry Arend Provo, Cindy Setum, Lucinda Klann, Nathan Burkhart, and Caleb Sorenson (Roseville, MN, USA).

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Conflicts of interest

TPA, RJF, MAW, BDM, RAS, RMD, and MLO all received grant funds to their respective institutions for services related to patient enrolment, follow-up and data management for this clinical study; RGH received consulting fees for statistical analyses (US National Institutes of Health [NIH] R44-HL065851-03). KGL was co-inventor of the impedance-threshold device and active compression-decompression cardiopulmonary resuscitation device, and founded Advanced Circulatory Systems in 1997 after the University of Minnesota (MN, USA) declined the opportunity to apply for patent protection on the impedance threshold device. All investigators feel KGL contributed substantially to this study and therefore should be listed as an author rather than incorporating his role within the activities of the sponsor, Advanced Circulatory Systems. In his role as the Chief Medical Officer of Advanced Circulatory Systems, KGL participated with the other investigators in obtaining the NIH grant funding (KGL was the principal investigator on the Small Business Innovation Research grant), the study design, data interpretation, writing and the decision to submit the paper for publication. KGL was not involved in any patient care or assessment of patient neurological status during the 1-year follow-up. Outside the present study, TPA has board membership for Take Heart America and Citizen CPR Foundation, has consulted for JoLife Medical and Medtronic Foundation, and has received grants/grants pending from the NIH Immediate Trial, NIH Resuscitation Outcomes Consortium, NIH Neurological Emergency Treatment Trials Network, and NIH Medical College of Wisconsin K12 Research Career Development Program. RJF has received payment for one lecture from Advanced Circulatory Systems. MAW has consulted for Baxter and Vitacare, has received grants/grants pending from the NIH Immediate Trial, payment for lectures or speakers' bureau membership from Vitacare and Sub Zero, and royalties from Cook Critical Care. BDM has board membership for Take Heart Minnesota and has received grants/grants pending from the NIH Neurological Emergency Treatment Trials Network. DET has received grants/grants pending from the Predict HD study, NINDS-6375, NINDS-40068 and NIMH-01579, and royalties as a textbook editor.

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