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Clinical paper

Treatment of non-traumatic out-of-hospital cardiac arrest with active compression decompression cardiopulmonary resuscitation plus an impedance threshold device☆

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ABSTRACT

Background: A recent out-of-hospital cardiac arrest (OHCA) clinical trial showed improved survival to hospital discharge (HD) with favorable neurologic function for patients with cardiac arrest of cardiac origin treated with active compression decompression cardiopulmonary resuscitation (CPR) plus an impedance threshold device (ACD + ICD) versus standard (S) CPR. The current analysis examined whether treatment with ACD + ITD is more effective than standard (S-CPR) for all cardiac arrests of non-traumatic origin, regardless of the etiology.

Methods: This is a secondary analysis of data from a randomized, prospective, multicenter, intention-to-treat, OHCA clinical trial. Adults with presumed non-traumatic cardiac arrest were enrolled and followed for one year post arrest. The primary endpoint was survival to hospital discharge (HD) with favorable neurologic function (Modified Rankin Scale score ≤ 3).

Results: Between October 2005 and July 2009, 2738 patients were enrolled (S-CPR = 1335; ACD + ITD = 1403). Survival to HD with favorable neurologic function was greater with ACD + ITD compared with S-CPR: 7.9% versus 5.7%, (OR 1.42, 95% CI 1.04, 1.95, $p = 0.027$). One-year survival was also greater: 7.9% versus 5.7%, (OR 1.43, 95% CI 1.04, 1.96, $p = 0.026$). Nearly all survivors in both groups had returned to their baseline neurological function by one year. Major adverse event rates were similar between groups.

Conclusions: Treatment of out-of-hospital non-traumatic cardiac arrest patients with ACD + ITD resulted in a significant increase in survival to hospital discharge with favorable neurological function when compared with S-CPR. A significant increase survival rates was observed up to one year after arrest in subjects treated with ACD + ITD, regardless of the etiology of the cardiac arrest.

1. Introduction

Use of active compression decompression cardiopulmonary resuscitation (CPR) plus an impedance threshold device (ACD + ICD) has been shown in animal studies to increase myocardial and cerebral perfusion and to improve neurological outcome.[1] A recent

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clinical trial called the ResQTrial demonstrated that ACD + ITD improved survival to hospital discharge with favorable neurologic function for subjects with an OHCA of presumed cardiac etiology by 53%, compared with S-CPR.[2] This study focused on cardiac arrest of presumed cardiac etiology. After resuscitation efforts were completed, many patients in that trial were found to have had one or more exclusionary criteria, such as a cardiac arrest of non-cardiac etiology.

Given the need to start CPR as soon as possible to optimize chances for survival, widespread implementation of ACD + ITD would require immediate application of this intervention to a wide spectrum of patients with cardiac arrest, often before the cause of the cardiac arrest is known. One of the primary reasons for performing the analysis described in this manuscript was to determine whether rescue personnel should know the etiology of the cardiac arrest *before* providing ACD + ITD therapy. We know that it is difficult in many cases and impossible in others to know the etiology prior to starting CPR. Thus, the primary objective of this secondary analysis of the ResQTrial study population was to determine whether treatment with ACD + ITD is more effective in returning patients to their baseline neurological function than S-CPR in all randomized study subjects, regardless of the cause of the arrest. The primary outcome measure was survival to hospital discharge with favorable neurological function, as determined by the Modified Rankin Scale.

2. Methods

The ResQTrial was performed by investigators in seven distinct geographic locations in the United States (US), including 46 emergency medical services (EMS) agencies, encompassing a total population of 2.3 million. The study was conducted under the US Code of Federal Regulations (21 CFR 50.24): Exception from Informed Consent under Emergency Circumstances. Informed consent was required for continued participation in the study, which consisted of medical records review and in-person follow-up neurological assessments. The protocol was implemented under an Investigational Device Exemption provided by the US Food and Drug Administration and approved by 25 Institutional Review Boards (IRBs). Both devices (ResQPUMP®; ResQPOD® ITD 16) are manufactured by Advanced Circulatory Systems, Inc., Roseville, MN, USA.

2.1. Study population

Adults (≥18 years of age) with presumed non-traumatic OHCA of all potential aetiologies were eligible for randomization. Patients were not randomized by EMS providers for the following reasons: <18 years of age, pre-existing DNR orders, evidence of a traumatic arrest, signs of obvious clinical death, experienced an in-hospital cardiac arrest, conditions that precluded the use of CPR, or a recent sternotomy. After randomization, patients received CPR regardless of the cause of the non-traumatic cardiac arrest. These subjects comprised the intention-to-treat (ITT) population (all subjects randomized in the trial, regardless of the presumed etiology). The initial analysis published in the Lancet focused on a subgroup of this ITT population that were found to have a cardiac arrest of presumed cardiac etiology.[2] This determination was made by the site investigators and coordinators after comprehensive review of the medical record. This determination was then reviewed and adjudicated by an independent Clinical Event Committee in a blinded manner. The following conditions were excluded from the primary analysis but were included in this current analysis: cardiac arrest of non-cardiac origin (respiratory cause, non-traumatic hemorrhage, stroke, metabolic abnormality, drug overdose, electrocution, or other non-cardiac causes); CPR by EMS personnel provided for <1 min; complete airway obstruction that could not be cleared or attempts at advanced airway management that were unsuccessful; intubation with a leaky or uncuffed advanced airway device; or a stoma, tracheotomy, or tracheostomy. Additionally, patients from the pre-determined run-in phase, who were enrolled using the same protocol as the pivotal phase, were included in this analysis.

2.2. Randomization and resuscitation procedures

A detailed description of patient randomization and resuscitation procedures have been previously reported.[2] These procedures were followed for all patients included in this analysis. Briefly, patients were assigned to ACD + ITD or S-CPR study groups on a 1:1 proportional basis using a cluster randomization plan that prospectively determined which method of CPR would be used based upon a weekly block randomization schedule at each clinical site. A run-in phase preceded the pivotal phase to assure that study logistics were well coordinated and that both CPR methods were being performed correctly. In the run-in phase, patients were randomized, entered into the study, and underwent follow-up evaluation to one year according to the same protocol used in the pivotal phase (main study).

CPR was initiated by basic life support (BLS) or advanced life support (ALS) EMS providers consistent with local policies and procedures per the 2005 American Heart Association (AHA) Guidelines.[3] In all cases, chest compressions were started as soon as the patient was determined to be in cardiac arrest. S-CPR was delivered at 100 compressions per minute, with ACD + ITD CPR performed at 80 compressions per minute. Rescuers were instructed to immediately attach the ITD on arrival at the patient, between the ventilation bag and the facemask (maintaining a continuously tight seal using a two-handed technique), and relocated it to the advanced airway, once established. During BLS, the compression:ventilation ratio was 30:2 and during ALS ventilations were performed asynchronously with the compression at a rate of 10/min. A timing light on the ITD that flashed at 10 times per minutes was used to provide the rescuers guidance about the ventilation rate. The ITD was to be removed when the patient had return of spontaneous circulation (ROSC), and reapplied if re-arrest occurred. The study devices were carried by all rescuers. CPR was performed at the scene and rescuers were encouraged to perform CPR for at least 30 min, unless ROSC occurred. Use of study devices was discontinued at the time of transfer of patient care to hospital staff.

2.3. Outcome measures

Neurologic assessment using the Modified Rankin Scale (MRS), Cerebral Performance Category (CPC) and Overall Performance Category (OPC) was performed at the time of hospital discharge.[4,5] CPC, OPC, and Disability Rating Scale (DRS) score were assessed at 30 days, 90 days, and one year. In addition, Cognitive Abilities Screening Instrument (CASI, Version E-1.1) and Beck Depression Inventory (BDI, version II) were also assessed at 90 days and one year.[6–8] The assessment tools were administered by qualified study nurses who were trained under the direction of a neuropsychologist (DT). The primary endpoint was survival to hospital discharge with favorable neurologic function, defined as a MRS score ≤ 3. The CPC was assessed at all follow-up intervals and was used as the basis for a general comparison of neurologic function over time. A CPC score ≤ 2 was regarded as evidence of favorable neurologic function.

Safety was assessed as the overall rate of major adverse events through hospital discharge. Major adverse events included: death, cerebral bleeding, bleeding requiring transfusion or surgery,

seizure, rearrest, pulmonary edema, rib/sternal fracture, and internal organ injury.

2.4. Blinding

With the exception of CPR performance by EMS personnel, all other aspects of the study, including obtaining patient consent, in-hospital patient care, review of medical records, and administration of neurologic evaluations, were executed by research staff that were blinded to the method of CPR. Use of ACD resulted in chest bruising that may have unblinded some in-hospital care providers to the method of CPR, although we are unable to quantify the impact of potential unblinding on the primary outcome. The data and safety monitoring board (DSMB) and clinical events committee (CEC) also remained blinded throughout the entire enrollment phase of the study.

2.5. Data management and quality assurance

Data were collected according to the Utstein Guidelines from the EMS run reports for all patients, and from hospital records and neurologic assessment surveys for all consented patients.[9] Monitoring was performed throughout the study to ascertain protocol adherence, patient consent, and completion of data forms. An independent DSMB reviewed safety and interim progress throughout the study. An independent CEC was responsible for the adjudication of all adverse events and all cases that were excluded from the primary analysis population. When consent was denied, public documents, including public death records, were reviewed to assess patient survival status.

2.6. Statistical analysis

This analysis was performed on an intention-to-treat basis, and includes all subjects randomized to S-CPR or ACD + ITD during the run-in phase and pivotal phase. Patients enrolled in the previously described third exploratory arm of the study are not included.[2] Statistical analyses were performed by an independent biostatistician, in accordance with the original study protocol. Differences between study groups were assessed using Fisher's exact tests and Student's *t* tests. Associated *p*-values were unadjusted for multiplicity and regarded as nominal values. Patients with unknown survival status or who were known to be alive but were missing responses for the neurologic assessments were not included in the analysis. For analysis of CASI and DRS results, mean scores in the two study groups were compared. The proportion of patients in each group with one or more major adverse events was also analyzed. Survival outcomes were evaluated using Kaplan–Meier actuarial analyses. StatXact version 8, SPSS version 18.0, and MIX 2.0 Pro were used for the statistical analyses.

3. Results

From October 2005 to July 2009, a total of 2738 patients were prospectively enrolled and randomized to treatment with ACD + ITD ($N = 1403$) or S-CPR ($N = 1335$) (Fig. 1). Among all survivors to hospital discharge, consent for ongoing participation in the study was obtained in 86.0% (257/299). Known survival outcomes to one year were available for 2669 (97.5%) patients. Baseline demographics and a summary of resuscitation efforts are shown in Table 1. Baseline characteristics were similar and enrollment was balanced between groups at all sites. There was no difference in the probability of a cardiac arrest victim being randomized into the study based on the assigned treatment week (S-CPR, 49.86% (2924/5865) vs. ACD + ITD, 50.14%, (2941/5865); $p = 0.8345$). Randomized subjects also had the same probability of being enrolled in the two study groups (S-CPR, 45.66% (1335/2924) vs. ACD + ITD, 47.70% (1403/2941); $p = 0.12$. There was, however, a difference in the proportions of subjects for whom resuscitation was attempted (S-CPR, 54.34% (1589/2924) vs. ACD + ITD, 57.40% (1688/2941); $p = 0.019$), suggesting a potential bias by emergency personnel to enroll subjects and use the devices, when available, in cases where S-CPR might not have been applied. There were no significant differences between study groups in the proportions of in-hospital treatments for admitted patients.

Table 1
Baseline demographics and resuscitation efforts.[a]

Parameter	S-CPR [*N* = 1335]	ACD + ITD [N = 1403]
Age, mean, years:	64.5 (17.2)	63.2 (17.8)
18–34	70 (5.2%)	92 (6.6%)
35–44	99 (7.4%)	129 (9.2%)
45–54	193 (14.5%)	235 (16.7%)
55–64	295 (22.1%)	258 (18.4%)
65–74	256 (19.2%)	244 (17.4%)
75–84	246 (18.4%)	287 (20.5%)
≥85	175 (13.1%)	157 (11.2%)
Data not available	1 (0.07%)	1 (0.07%)
Gender, male	827 (61.9%)	882 (62.9%)
Arrest witnessed	732 (54.8%)	764 (54.5%)
Arrest unwitnessed	601 (45.0%)	632 (45.0%)
Data not available	2 (0.1%)	7 (0.5%)
Bystander CPR provided	533 (39.9%)	585 (41.7%)
Data not available	1 (0.07%)	2 (0.1%)
Initial cardiac arrest rhythm:		
Ventricular fibrillation/pulseless ventricular tachycardia	318 (23.8%)	371 (26.4%)
Asystole	673 (50.4%)	696 (49.6%)
Pulseless electrical activity	326 (24.4%)	318 (22.7%)
Data not available	18 (1.3%)	18 (1.3%)
911 to first response time, min	5.3 (2.8)	5.2 (2.8)
911 to EMS CPR start time, min[b]	6.6 (3.5)	6.6 (3.3)
Advanced airway during EMS CPR (endotracheal intubation or supraglottic airway)	1144 (85.7%)	1231 (87.7%)
Data not available	4 (0.3%)	4 (0.3%)
911 to placement of study device, min	–	7.1 (3.5)
ROSC during pre-hospital CPR	537 (40.2%)	591 (42.1%)
Adrenaline (epinephrine) (1:10,000), mg	3.02 (2.17)	3.08 (2.12)
patients without ROSC	3.36 (2.15)	3.51 (2.06)
Duration of CPR, min	25.5 (12.9)	26.4 (12.4)
Duration CPR, patients without ROSC	29.4 (11.6)	30.5 (10.5)
Admitted to hospital	376 (28.2%)	431 (30.7%)
In-hospital hypothermia, % of admitted	139 (37.0%)	147 (34.1%)
Cardiac catheterization, % of admitted	89 (23.7%)	126 (29.2%)
Coronary stenting, % of admitted	29 (7.7%)	46 (10.7%)
Coronary bypass surgery, % of admitted	8 (2.1%)	15 (3.5%)
Implanted cardio-defibrillator, % of admitted	38 (10.1%)	50 (11.6%)

[a] Values are expressed as number of patients (%) or mean (SD). ROSC = return of spontaneous circulation.
[b] These data do not include subjects with an EMS witnessed arrest.

Treatment with ACD + ITD resulted in a 38% relative increase in survival to hospital discharge with MRS ≤ 3 (primary endpoint), compared with S-CPR (Odds ratio 1.42, 95% CI 1.04,1.95; $p = 0.027$) (Table 2). Consistent differences between study groups in achievement of the primary endpoint were observed throughout the study (data not shown), and were independent of age, study site, gender, initial recorded cardiac rhythm, time from 911-to-CPR start, or whether the arrest was witnessed (Fig. 2). Overall, achievement of the primary endpoint was dependent on the time from 911 call to the start of randomized CPR treatment: there was only one survivor (in the ACD + ITD group) with MRS ≤ 3 when CPR was initiated more than 10 min after the 911 call for help by EMS personnel.

Neurological status in all patients who survived and who consented to participate in the follow up neurological testing demonstrated improvement in neurological functionality in both study groups (Table 2). Although significantly more patients

Table 2
Effectiveness and safety outcome measures[a] *n* (%).

Assessment	S-CPR [*N* = 1335]	ACD + ITD [*N* = 1403]	*p*-Value
Hospital discharge			
Survival to hospital discharge	134 (10.1%)	165 (11.8%)	0.159
Survival data not available	8 (0.6%)	5 (0.4%)	
Survival to hospital discharge with MRS ≤3[b]	75 (5.7%)	110 (7.9%)	0.027
MRS scores at hospital discharge:			
0	9 (0.7%)	19 (1.4%)	0.053
1	12 (0.9%)	20 (1.4%)	
2	34 (2.6%)	38 (2.7%)	
3	20 (1.4%)	33 (2.3%)	
4	18 (1.4%)	21 (1.5%)	
5	32 (2.4%)	32 (2.3%)	
6	1193 (90.0%)	1233 (88.0%)	
Survived, MRS data not available	9 (0.7%)	2 (0.1%)	
CPC scores at hospital discharge, CPC ≤ 2[c]:	83 (6.3%)	112 (8.0%)	0.087
Scores by group:			
1	49 (3.7%)	63 (4.5%)	0.067
2	34 (2.6%)	49 (3.5%)	
3	23 (1.7%)	36 (2.6%)	
4	19 (1.4%)	14 (1.0%)	
5	1193 (89.9%)	1233 (88.2%)	
Survived, CPC data not available	9 (0.7%)	3 (0.2%)	
OPC scores at hospital discharge[d]; *Scores by group*:			
1	31 (2.3%)	38 (2.7%)	0.067
2	43 (3.2%)	62 (4.4%)	
3	32 (2.4%)	48 (3.4%)	
4	19 (1.4%)	14 (1.0%)	
5	1193 (89.9%)	1233 (88.2%)	
Survived, OPC score not available	9 (0.7%)	3 (0.2%)	
30 days			
Survival to 30 days	105 (8.0%)	146 (10.5%)	0.024
Survival data not available	19 (1.4%)	15 (1.1%)	
CPC scores at 30 days, CPC ≤ 2:	76 (5.8%)	94 (6.9%)	0.268
Scores by group:			
1	51 (3.9%)	70 (5.0%)	0.067
2	25 (1.9%)	24 (1.7%)	
3	9 (0.7%)	24 (1.7)	
4	8 (0.6%)	6 (0.4%)	
5	1211 (92.0%)	1242 (89.5%)	
Survived, CPC data not available	12 (0.9%)	22 (1.6%)	
OPC scores at 30 days; *Scores by group*:			
1	35 (2.7%)	50 (3.6%)	0.068
2	35 (2.7%)	33 (2.4%)	
3	15 (1.1%)	35 (2.5%)	
4	8 (0.6%)	6 (0.4%)	
5	1211 (92.0%)	1242 (89.5%)	
Survived, OPC data not available	12 (0.9%)	22 (1.6%)	
Disabilities rating score at 30 days for completers:	5.67 (7.84) (*n* = 87)	5.59 (7.24) (*n* = 123)	0.938
DRS by category:			
None	24 (27.6%)	32 (26.0%)	0.848
Mild	5 (5.7%)	9 (7.3%)	
Partial	23 (26.4%)	29 (23.6%)	
Moderate	16 (18.4%)	19 (15.4%)	
Moderately severe	5 (5.7%)	17 (13.8%)	
Severe	4 (4.6%)	5 (4.1%)	
Extremely severe	2 (2.3%)	4 (3.3%)	
Vegetative	0	0	
Extreme vegetative	8 (9.2%)	8 (6.5%)	
90 days			
Survival to 90 days	94 (7.2%)	130 (9.4%)	0.036
Survival data not available	26 (1.9%)	24 (1.7%)	
CPC scores at 90 days, CPC ≤ 2:	72 (5.5%)	98 (7.2%)	0.082
Scores by group:			
1	57 (4.4%)	84 (6.1%)	0.084
2	15 (1.1%)	14 (1.0%)	
3	4 (0.3%)	9 (0.7%)	
4	7 (0.5%)	3 (0.2%)	
5	1215 (92.8%)	1249 (90.6%)	
Survived, CPC data not available	11(0.8%)	20(1.5%)	
OPC scores at 90 days; *Scores by group*:			
1	48 (3.7%)	68 (4.9%)	0.088
2	20 (1.5%)	23 (1.7%)	
3	8 (0.6%)	16 (1.2%)	
4	7 (0.5%)	3 (0.2%)	
5	1215 (92.8%)	1249 (90.6%)	

Table 2 (*Continued*)

Assessment	S-CPR [*N* = 1335]	ACD + ITD [*N* = 1403]	*p*-Value
Survived, OPC data not available	11 (0.8%)	20 (1.5%)	
Beck Depression Inventory at 90 days, mean score	6.29 (6.44)	7.63 (7.38)	0.239
Cognitive Abilities Screening Instrument at 90 days Mean score	92.11 (9.15)	91.14 (11.74)	0.612
Disabilities rating score at 90 days for completers:	4.33 (7.62)	3.59 (6.27)	0.468
Mean score	(*n* = 78)	(*n* = 107)	
None	32 (41.0%)	40 (37.4%)	
Mild	11 (14.1%)	17 (15.9%)	
Partial	12 (15.4%)	22 (20.6%)	
Moderate	9 (11.5%)	12 (11.2%)	0.991
Moderately severe	6 (7.7%)	8 (7.5%)	
Severe	0	0	
Extremely severe	1 (1.3)%	3 (2.8%)	
Vegetative	1 (1.3%)	1 (0.9%)	
Extreme vegetative	6 (7.7%)	4 (3.7%)	
One year			
Survival to one year	74 (5.7%)	108 (7.9%)	0.026
Survivors with VF as the initial recorded cardiac rhythm (at time of index cardiac arrest)	50 (16.8%)	81 (23.2%)	0.050
Survival data not available	32 (2.4%)	37 (2.6%)	
CPC scores at 1 year, CPC ≤2:	61 (4.7%)	86 (6.4%)	0.062
Scores by group:			
1	52 (4.0%)	73 (5.3%)	0.076
2	9 (0.7%)	13 (1.0%)	
3	4 (0.3%)	3 (0.2%)	
4	2 (0.2%)	3 (0.2%)	
5	1229 (94.3%)	1258 (92.1%)	
Survived, CPC data not available	7 (0.5%)	16 (1.2%)	
OPC scores at 1 year; *Scores by group*:			
1	47 (3.6%)	60 (4.4%)	0.081
2	12 (0.9%)	22 (1.6%)	
3	6 (0.5%)	7 (0.5%)	
4	2 (0.2%)	3 (0.2%)	
5	1229 (94.3%)	1258 (92.1%)	
Survived, OPC data not available	7 (0.5%)	16 (1.2%)	
Beck Depression Inventory at 1 year, mean score	6.43 (6.96)	6.08 (5.83)	0.750
CASI at 1 year, mean score	91.98 (12.98)	92.38 (11.68)	0.868
Disabilities Rating Score at 1 year for completers:	2.52 (5.27) (*n* = 62)	2.94 (5.99) (*n* = 89)	0.651
DRS categories:			
None	33 (53.2%)	44 (49.4%)	0.607
Mild	7 (11.3%)	7 (7.9%)	
Partial	10 (16.1%)	19 (21.3%)	
Moderate	7 (11.3%)	8 (9.0%)	
Moderately severe	2 (3.2%)	5 (5.6%)	
Severe	0	0	
Extremely severe	1 (1.6%)	2 (2.2%)	
Vegetative	0	0	
Extreme vegetative	2 (3.2%)	4 (4.5%)	
Major adverse events through hospital discharge			
Patients with reported adverse events through hospital discharge:			
≥1 reported AE	1253 (93.9%)	1320 (94.1%)	0.810
0	82 (6.1%)	83 (5.9%)	
Events type:			
Death	1195 (89.5%)	1234 (88.0%)	0.205
Rearrest	249 (18.7%)	289 (20.6%)	0.211
Cardiac tamponade	4 (0.3%)	8 (0.6%)	0.388
Cerebral bleeding/thrombus	11 (0.8%)	13 (0.9%)	0.839
Pneumothorax/hemothorax	14 (1.0%)	18 (1.3%)	0.598
Internal organ injury	5 (0.4%)	6 (0.4%)	1.000
Pulmonary edema[e]	105 (7.9%)	159 (11.3%)	0.002
Seizure	20 (1.5%)	27 (1.9%)	0.462
Rib/sternal fracture	24 (1.8%)	22 (1.6%)	0.658
Bleeding requiring transfusion or surgery	8 (0.6%)	19 (1.4%)	0.053
Aspiration	21 (1.6%)	18 (1.3%)	0.629

[a] Values are expressed as number of patients (%) or mean (SD), as applicable. MRS = Modified Rankin Scale; CPC = Cerebral Performance Category; OPC = Overall Performance Category; CASI = Cognitive Abilities Screening Inventory; DRS = Disabilities Rating Scale.

[b] MRS 0 = no symptoms; MRS 1 = no significant disability; MRS 2 = slight disability; MRS 3 = moderate disability; MRS 4 = moderately severe disability; MRS 5 = several disability; MRS 6 = death. $p = 0.053$ for Mann–Whitney test for comparison of MRS by group.

[c] CPC 1 = Good cerebral performance, might have mild neurologic or psychological deficit; CPC 2 = Moderate cerebral disability, sufficient cerebral function for independent activities of daily life; CPC 3 = Severe cerebral disability, dependent on others for daily support; CPC 4 = Coma or vegetative state; CPC 5 = brain death or traditional death. There were no patients classified as brain dead in the study. $p = 0.067$ for Mann–Whitney test for comparison of CPC by group.

[d] OPC1 = Good overall performance. Healthy, alert, capable of normal life. Good cerebral performance (CPC 1) plus no or only mild functional disability from non-cerebral organ system abnormalities; OPC2 = Moderate overall disability. Moderate cerebral disability alone (CPC 2) or moderate disability from noncerebral system dysfunction alone or both. Performs independent activities of daily life (dressing, traveling, and food preparation). May be able to work part-time in sheltered environment but disabled for competitive work; OPC3 = 3 Severe overall disability. Conscious. Severe cerebral disability alone (CPC 3) or severe disability from non-cerebral organ system dysfunction alone or both. Dependent on others for daily support; OPC4 = Same as CPC 4; OPC 5 = Same as CPC 5.

[e] Pulmonary edema included pre-hospital reports of fluid or secretions in the airway and/or pulmonary edema or pleural effusion reported by X-ray or CT imaging.

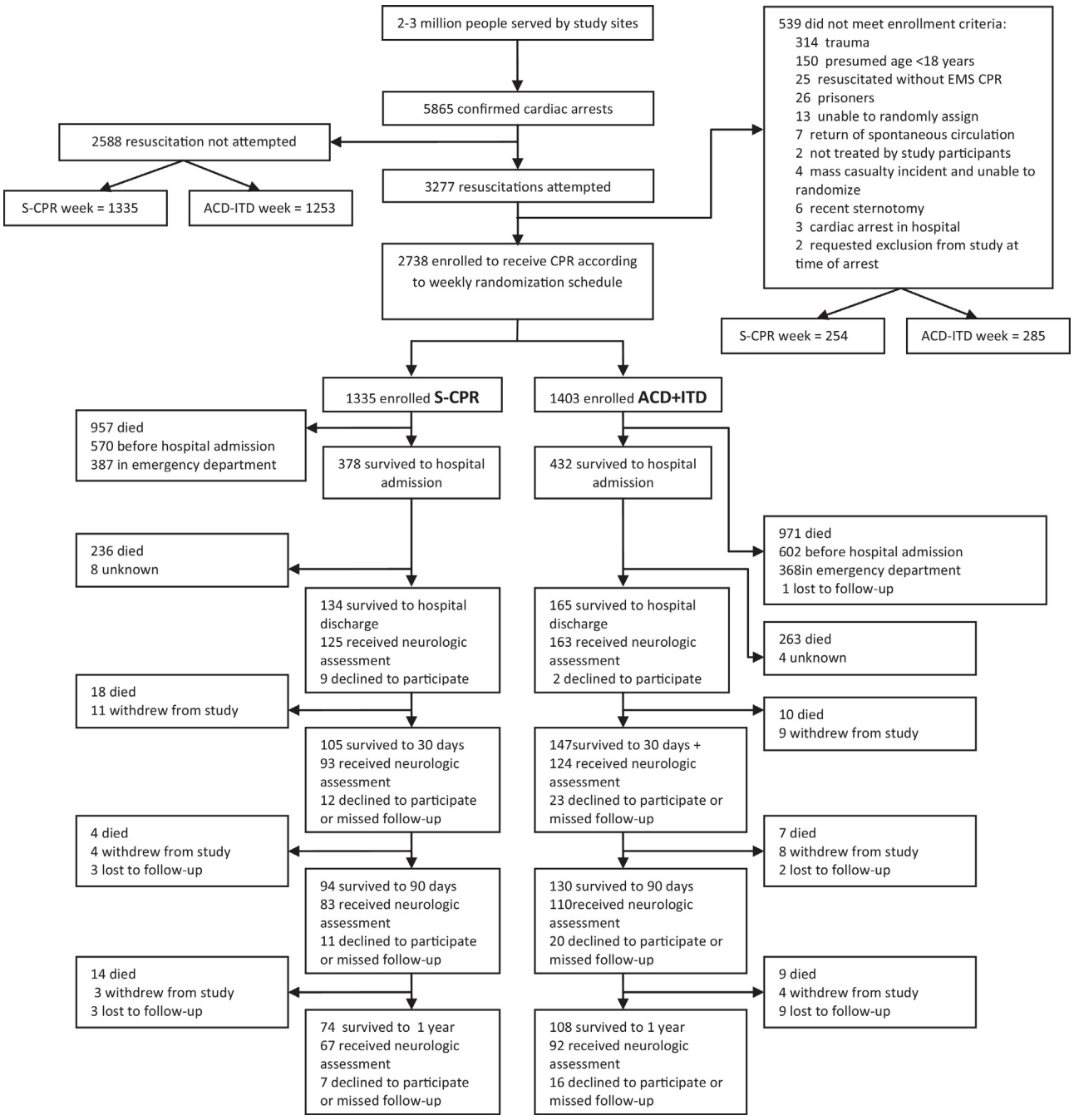

Fig. 1. Study population. Figure shows progression of all enrolled patients throughout the study duration (includes 268 patients randomized in the run-in phase, 134 in each arm). Public records were searched at one year for all patients who had withdrawn from the study or were lost to follow-up. DNR = do not resuscitate. EMS = emergency medical services. CPR = cardiopulmonary resuscitation. S-CPR = standard CPR. ACD + ITD = active compression decompression CPR with combined used of an impedance threshold device.

survived to one year in the ACD + ITD group, neurological function was similar among all long-term survivors regardless of the method of CPR by EMS. There was no evidence that ACD + ITD increased the number of survivors with significant neurological impairment. Further analysis revealed that the MRS ($\leq$3 vs. >3) assessment at the time of hospital discharge was highly predictive of whether or not a patient would be alive and with favorable neurological function (CPC score ≤ 2) at one year (98.0% observed agreement, kappa = 0.800, $p < 0.001$).

Among all randomized patients in the run-in and main study populations, there were 522 in the S-CPR group and 561 in the ACD + ITD group who were excluded from the previously reported primary study analysis as they had a cardiac arrest with a non-cardiac etiology [e.g. pulmonary emboli, respiratory arrest, drug overdose]: they were included in the current analysis.[2] Survival and neurologic outcomes for this subgroup of patients with a non-traumatic cardiac arrest from a non-cardiac etiology, that were not included in the primary analysis, are shown separately in Table 3. Of these, 6.3% (35/558) treated with ACD + ITD had a MRS ≤ 3 at the time of hospital discharge, compared with 5.4% (28/518) treated with S-CPR, $p = 0.604$. At one year, 4.5% (24/537) of those treated with ACD + ITD survived with CPC ≤ 2, compared with 3.6% (18/505) treated with S-CPR ($p = 0.529$); 24 patients in the ACD + ITD group and 17 patients in the S-CPR group had unknown CPC scores

Table 3
Outcomes in the subgroup of patients enrolled and excluded from the primary analysis.[a]

Randomized CPR treatment in patients excluded from primary analysis	Survival to hospital discharge	MRS at hospital discharge (distribution of scores)	CPC at hospital discharge (distribution of scores)	Survival to one year	CPC at One year (distribution of scores)
S-CPR (n = 522)	54 (unknown = 2)	MRS 0–6 MRS 1–4 MRS 2–8 MRS 3–10 MRS 4–8 MRS 5–16 MRS 6–466 MRS not available – 4	CPC 1–14 CPC 2–15 CPC 3–13 CPC 4–9 CPC 5–466 CPC not available – 5	26 (unknown = 13)	CPC 1–14 CPC 2–4 CPC 3–2 CPC 4–2 CPC 5–483 CPC not available – 17
ACD + ITD CPR (n = 561)	60 (unknown = 3)	MRS 0–8 MRS 1–9 MRS 2–8 MRS 3–10 MRS 4–11 MRS 5–14 MRS 6–498 MRS not available – 3	CPC 1–18 CPC 2–19 CPC 3–18 CPC 4–5 CPC 5–498 CPC not available – 3	34 (unknown = 17)	CPC 1–17 CPC 2–7 CPC 3–2 CPC 4–1 CPC 5–510 CPC not available – 24

[a] The primary analysis population included patients with cardiac arrest due to cardiac aetiology[2]. All cases excluded from the primary analysis population were adjudicated by an independent clinical events committee. Data also include subjects from the run-in phase who did meet all final inclusion criteria. Three ACD + ITD patients and four S-CPR patients had unknown MRS score because consent to review the medical record was denied.

because consent to review the medical record was denied or the subject was lost to follow up. Among all randomized patients discharged alive or confirmed alive at 30 days, survival to one year was greater in the ACD + ITD group: 82.1% vs 69.7%, (p = 0.014) (Fig. 3).

Overall, there was no difference in the rate of major adverse events between groups. However, pulmonary edema was more common in the ACD + ITD group (Table 2). In the subgroup of patients with pulmonary edema, survival to hospital discharge with MRS ≤ 3 was 11.3% (18/159) with ACD + ITD, versus 11.7% (12/103) in the S-CPR group; whereas in patients without pulmonary edema, survival to hospital discharge with MRS ≤ 3 was 7.4% (92/1237) with ACD + ITD versus 5.2% (63/1215) with S-CPR. There were seven patients without pulmonary edema in the ACD + ITD group, and 15 patients without pulmonary edema and two patients with pulmonary edema in the S-CPR group for whom MRS status at hospital discharge was unknown.

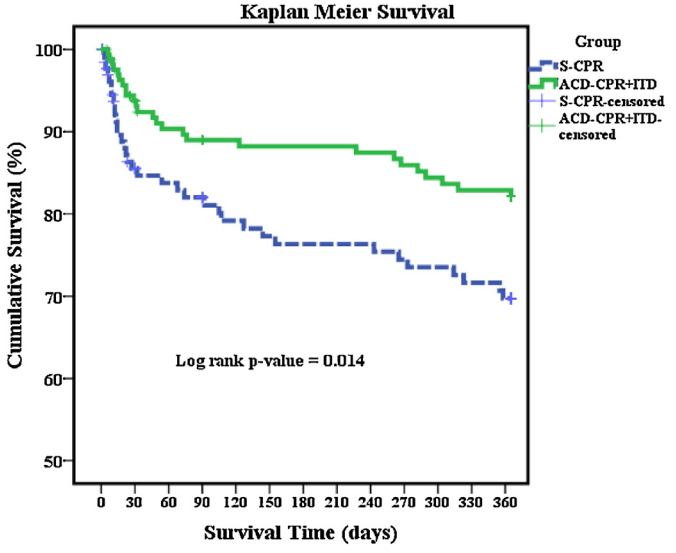

Fig. 2. Kaplan–Meier survival [all subjects discharged alive or alive at 30 days]. Among all randomized patients discharged alive or confirmed alive at 30 days, survival to one year was greater in the ACD + ITD group: 82.1% versus 69.7%, p = 0.014 [log rank (Mantel–Cox) test of equality of survival distributions for the different levels of group]. Public death records were searched when consent for chart review and/or study inclusion could not be obtained from a subject or a subject's family. As a result we are able to report with accuracy subject survival status 30 days after cardiac arrest but not whether some subjects were discharged from the hospital alive.

4. Discussion

When EMS providers arrive at the scene of a cardiac arrest, they generally cannot distinguish between non-cardiac and cardiac etiology prior to initiating CPR. Given this limitation, the intent of this analysis was to determine if the observations from patients in cardiac arrest from a presumed cardiac etiology could be generalized to all non-traumatic cardiac arrest patients in need of CPR, regardless of the cause of the arrest. This study demonstrated that survival to HD with favorable neurological function rates were significantly increased when using ACD + ITD, as were one year survival rates, compared with S-CPR. There were similar rates of major adverse events between groups.

The current analyses also shed new light on which study endpoints best predict survival after OHCA. There are legitimate concerns that interventions which improve ROSC rates alone may only improve survivability, and not survivability with a good neurologic outcome. ROSC rates were similar between the two groups (Table 1), but significantly more patients in the ACD + ITD group survived to hospital discharge with favorable neurological function. Similarly, the one year survival rate was 7.9% with ACD + ITD compared with 5.7% in the S-CPR group. As such, ROSC rates should not be used when assessing the potential value of ACD + ITD CPR. ROSC rates have been previously shown to be a poor predictor of long-term survival for other CPR interventions such as use of adrenaline (epinephrine).[10] The lack of difference between in ROSC rates versus HD with MRS ≤ 3 rates may be due to other factors as well. In comparison to a prior study with ACD + ITD CPR[11] performed a decade earlier, where ROSC rates were reported to be higher in the device group versus S-CPR or ACD CPR alone, recent advances in S-CPR may have resulted in higher rates of cardiac resuscitation but inadequate brain recovery.

In contrast to the ROSC rate, the current analysis demonstrated that the neurological status at the time of hospital discharge, as measured by MRS, is highly predictive of who will survive for at least one year and of their long-term neurological function. The MRS was used as the primary endpoint outcome measure, in part because it takes into account the patient's prior health status. This is the first time that the MRS score at the time of hospital discharge has been demonstrated to predict long-term outcomes for

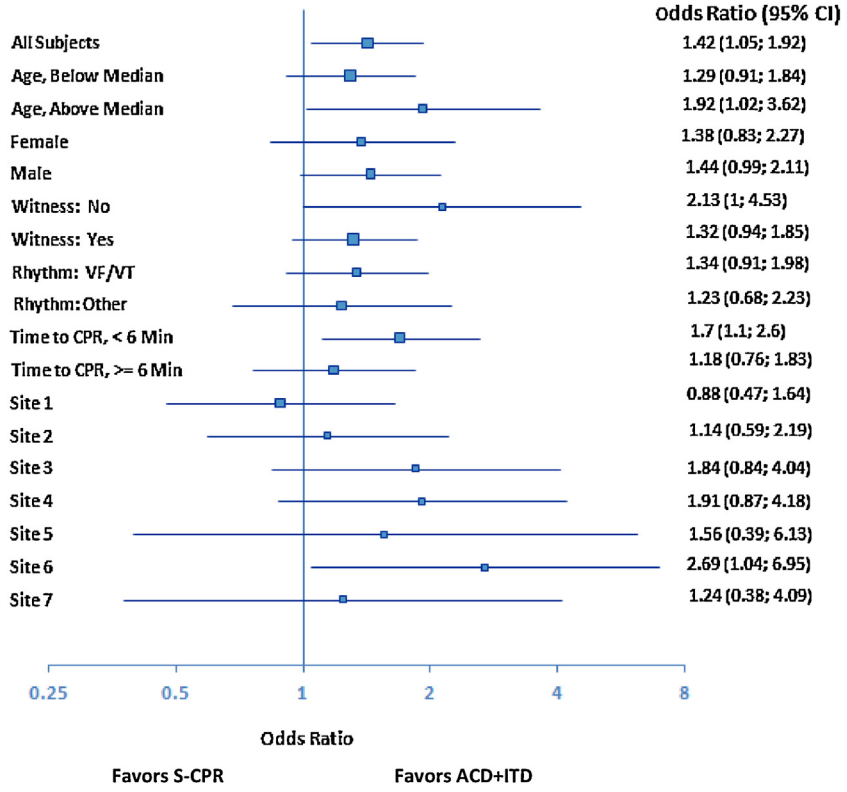

Fig. 3. Effects of age, gender, cardiac arrest surroundings, and study site on primary endpoint. Estimated odds ratios exceeded 1.00 for subgroups based on age, gender, cardiac arrest surroundings, and all study sites except for Site 1. VF/VT = ventricular fibrillation and pulseless ventricular tachycardia. CPR = cardiopulmonary resuscitation.

patients with a non-traumatic cardiac arrest. These observations are consistent with prior physiological studies in animals and in patients, demonstrating that modulation of intrathoracic pressure with ACD + ITD improves blood flow to the heart and brain and improves survival with favorable neurological function compared with S-CPR. The findings are also consistent with earlier clinical trials that demonstrated the mechanistic benefits of ACD + ITD CPR on intrathoracic pressure regulation, hemodynamics, and short-term survival.[11]

There was no difference in the overall rate of major adverse events; however, pulmonary edema was more common with ACD + ITD (Table 2). Patients with pulmonary edema in both treatment groups had higher survival rates than those without pulmonary edema. Thus, while it is possible that ACD + ITD caused negative pressure pulmonary edema by itself, this is unlikely based upon prior measurements of negative intrathoraicic pressure during ACD + ITD in patients in cardiac arrest.[12] We speculate spontaneous gasping may underlie the observations related to pulmonary edema in this study. Specifically, we postulate that patients in both groups with the highest levels of cerebral perfusion during CPR developed spontaneous gasping which can result in a marked decrease in negative intrathoracic pressure, especially when using an ITD, and consequently negative pressure pulmonary edema. Regardless of the cause of the pulmonary edema in this study, it is a treatable condition and was associated with a positive outcome.

Determining the etiology of cardiac arrest is often impossible until further information has been obtained following resuscitation interventions. The comprehensive results in this current report of all randomized cardiac arrest subjects treated with either S-CPR or ACD + ITD suggest that, regardless of the etiology of the non-traumatic OHCA, more patients will survive long term with favorable neurological function with this new method of CPR. It is noteworthy that this study was not designed or powered to evaluate whether ACD + ITD may potentially improve outcomes for patients in cardiac arrest of a non-cardiac etiology. However, with this caveat, use of this new approach was not found to be detrimental in this patient subgroup and it appears to provide a survival benefit that is at least as beneficial as S-CPR in this subgroup.

4.1. Study limitations

First, EMS rescuers were not blinded to the CPR method used, theoretically introducing the potential for entry bias. As noted in Section 3, there was no significant difference in the probability of receiving the control or intervention treatment for patients who suffered out of hospital cardiac arrest. Additionally, once randomized, patients also had an equal chance of receiving the control or intervention, showing the block randomization scheme was balanced. Second, post-resuscitation factors were not controlled in this study; however, reported post-resuscitation care was similar between groups. Third, given the unique circumstances for obtaining consent under emergency circumstances, follow-up data from some patients could not be obtained. Fourth, we could not establish the relative contribution of ACD CPR alone, the ITD alone, or the rescuer feedback elements that are incorporated into these device designs (e.g., timing lights to guide ventilations, metronome to guide chest compression rate, and a force gauge to guide compression depth) to the positive study outcome. Data from studies in animals and humans suggest that every component is necessary to record benefits with this combined approach.[2,11,13–15] Fifth, CPR quality was assessed during training and retraining of both methods of CPR but not during CPR. Nonetheless, results with S-CPR are comparable or superior to other pre-hospital studies when CPR quality was assessed.[16] Sixth, due to funding limitations, the study was stopped earlier than anticipated and additional data could have changed the primary findings related to patients in cardiac arrest of presumed cardiac etiology. Seventh, based upon the

randomization plan, an assumption was been made that the week of the study had no effect on outcome.

5. Conclusions

The expanded analysis with 2738 subjects represents one of the largest prospective interventional CPR trials to date evaluating one year survival and neurologic outcomes after non-traumatic cardiac arrest. Patients treated with ACD + ITD had a relative 38% increase in survival to hospital discharge with favorable neurologic function (MRS $\leq$ 3), compared with S-CPR, regardless of the etiology of their cardiac arrest. Survival to one year with favorable neurological function was also increased by a relative 39% in patients who had been treated with ACD + ITD. Nearly all survivors, regardless of the method of CPR, had returned to their baseline neurological function one year after OHCA. These findings provide the strongest evidence to date that application of ACD + ITD in a wide spectrum of patients with OHCA cardiac arrest can significantly increase long-term survival rates with restoration of baselines neurological function.

Conflicts of interest statement

TPA, RJF, MAW, BDM, RAS, RMD, and MLO all received grant funds to their respective institutions for services related to patient enrollment, follow-up and data management for this clinical study; Outside the present study, TPA has board membership for Take Heart America and Citizen CPR Foundation, has consulted for JoLife Medical and Medtronic, Inc., and has received grants/grants pending from the NIH Immediate Trial, NIH Resuscitation Outcomes Consortium, the NIH Neurological Emergency Treatment Trials Network, and Medtronic Foundation. RJF has received payment for one lecture from Advanced Circulatory Systems and has received grants/grants pending from the NIH Immediate Trial. RGH received consulting fees for the statistical analyses performed (US National Institutes of Health [NIH] R44-HL065851-03). MAW has consulted for Baxter and Vitacare, has received grants/grants pending from the NIH Immediate Trial, payment for lectures or speaking from the NIH Immediate Trial, payment for lectures or speaker's 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. CMS, LK and NB are employed by Advanced Circulatory Systems, Inc., the study sponsor and manufacturer of the study devices. KGL is Chief Medical Officer for Advanced Circulatory Systems. He participated with the other investigators in obtaining the NIH grant funding, and was the principal investigator on the NIH grant that funded the study. KGL was not involved in any patient care or assessment of patient neurological status. JGS, SSW, and DY – None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2013.05.002.

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