Manual Chest Compression vs Use of an Automated Chest Compression Device During Resuscitation Following Out-of-Hospital Cardiac Arrest

A Randomized Trial

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Context High-quality cardiopulmonary resuscitation (CPR) may improve both cardiac and brain resuscitation following cardiac arrest. Compared with manual chest compression, an automated load-distributing band (LDB) chest compression device produces greater blood flow to vital organs and may improve resuscitation outcomes.

Objective To compare resuscitation outcomes following out-of-hospital cardiac arrest when an automated LDB-CPR device was added to standard emergency medical services (EMS) care with manual CPR.

Design, Setting, and Patients Multicenter, randomized trial of patients experiencing out-of-hospital cardiac arrest in the United States and Canada. The a priori primary population was patients with cardiac arrest that was presumed to be of cardiac origin and that had occurred prior to the arrival of EMS personnel. Initial study enrollment varied by site, ranging from late July to mid November 2004; all sites halted study enrollment on March 31, 2005.

Intervention Standard EMS care for cardiac arrest with an LDB-CPR device (n=554) or manual CPR (n=517).

Main Outcome Measures The primary end point was survival to 4 hours after the 911 call. Secondary end points were survival to hospital discharge and neurological status among survivors.

Results Following the first planned interim monitoring conducted by an independent data and safety monitoring board, study enrollment was terminated. No difference existed in the primary end point of survival to 4 hours between the manual CPR group and the LDB-CPR group overall (N=1071; 29.5% vs 28.5%; *P*=.74) or among the primary study population (n=767; 24.7% vs 26.4%, respectively; *P*=.62). However, among the primary population, survival to hospital discharge was 9.9% in the manual CPR group and 5.8% in the LDB-CPR group (*P*=.06, adjusted for covariates and clustering). A cerebral performance category of 1 or 2 at hospital discharge was recorded in 7.5% of patients in the manual CPR group and in 3.1% of the LDB-CPR group (*P*=.006).

Conclusions Use of an automated LDB-CPR device as implemented in this study was associated with worse neurological outcomes and a trend toward worse survival than manual CPR. Device design or implementation strategies require further evaluation.

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Out-of-hospital cardiac arrest claims hundreds of thousands of lives annually in North America. Successful resuscitation depends on a coordinated set of actions including early cardiopulmonary resuscitation (CPR). High-quality CPR may be important for both cardiac and brain resuscitation.[1-3] In animal investigations, fewer interruptions of CPR before and after defibrillation have improved cardiac and neurological outcomes.[4-7] The order of resuscitation interventions may also be important, eg, survival may be improved by performing CPR by emergency medical services (EMS) personnel prior to defibrillation.[8,9]

See also pp 2629 and 2661.

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Observations of rescue personnel indicate that maintaining consistent compressions is a difficult task.[10] In the laboratory, trained paramedics provide shallower and slower compressions over time without noticing.[11,12] Chest compressions often do not achieve guideline recommendations with regard to depth, rate, and hands-off time.[13,14]

The desire to provide optimal chest compressions led to the development of automated mechanical chest compression devices. The AutoPulse Resuscitation System (ZOLL Circulation, Sunnyvale, Calif) is a load-distributing band (LDB) circumferential chest compression device with an electrically actuated constricting band on a short backboard and has been approved by the US Food and Drug Administration for use in attempted resuscitation of cardiac arrest. In pig models and in-hospital cardiac arrest in humans, this LDB-CPR device produces greater blood flow to the heart and brain than manual CPR by trained individuals or the automated mechanical piston CPR device.[15,16] Animal investigation has demonstrated a greater likelihood of neurologically intact survival in prolonged ventricular fibrillation cardiac arrest with LDB-CPR.[17]

In this study, the AutoPulse Assisted Prehospital International Resuscitation (ASPIRE) trial, we compared LDB-CPR with manual CPR during out-of-hospital cardiac arrest. We hypothesized that 4-hour survival would be greater among patients randomized to LDB-CPR compared with those randomized to manual CPR. Secondary outcomes were survival to hospital discharge and neurological function at hospital discharge.

METHODS

Study Design

The study was conducted in Calgary, Alberta; Columbus, Ohio; suburbs of Pittsburgh, Pa; Seattle, Wash; and Vancouver, British Columbia. Because of differences in the time course of ethics review and approval and EMS training schedules, initial study enrollment varied by site, ranging from late July to mid November 2004 (TABLE 1). All sites halted study enrollment on March 31, 2005.

Cost and the inconvenience of carrying the LDB-CPR device to episodes at which it would not be assigned dictated the use of cluster randomization with crossover. Clusters were based on an EMS station or group of stations and crossover occurred at specified time intervals (4 weeks to 2 months). The clustering unit was based on a combination of EMS system operational and design considerations to avoid arrival of both response teams assigned to manual CPR and to automated mechanical LDB-CPR. Within a given site, half of the clusters were randomized to the control (manual CPR) and half to the intervention (LDB-CPR) with subsequent alternation between the intervention and the control. The rotation period was chosen partly for convenience of device transfer, to ensure temporal balance during the trial, and to avoid cyclical phenomena.[18]

The study was conducted under the regulations for emergency exception from informed consent, which require each US site to inform its community of the proposed trial and seek its opinion.[19,20] Notification of individuals enrolled in the study is also required, and the community must be informed of the final results. At each site, including the coordinating center, the primary research review board responsible for guidance, review, and oversight of human subjects' protection approved the study. In addition, research review boards at most receiving hospitals also reviewed and approved the study to allow study personnel to provide timely notification to the patient or family.

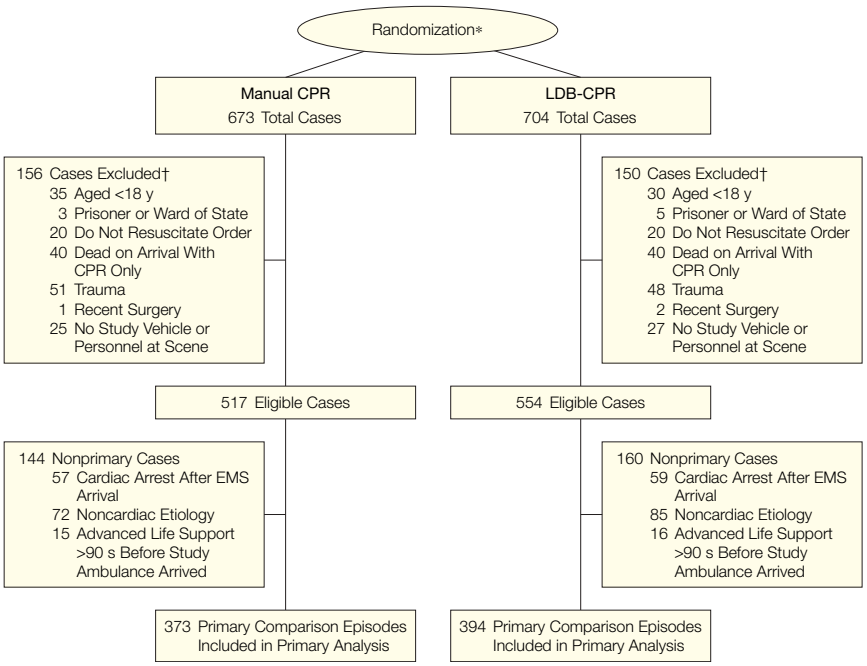
The study also convened an independent data and safety monitoring board consisting of a paramedic, an EMS physician, a biostatistician, and a

Table 1. Clusters and Enrollment by Site

	Participant Enrollment by Site					
	A (n = 314)	B (n = 111)	C (n = 201)	D (n = 346)	E (n = 99)	Total (N = 1071)
EMS system Tier*	1	2	2	2 + fire	2	
Historical survival rate, No./total (%)						
Ventricular fibrillation	4/25 (16)	6/42 (14.2)	31/101 (31)	NA	39/144 (27.1)‡	
All participants	5/115 (4.3)	NA	40/299 (13)	53/852 (6.2)	NA (9)	
No. of study vehicles†	34 ALS	28 ALS	47 BLS	43 BLS	35 ALS	187
No. of clusters	34 Vehicles	7 Agencies	2 Areas	4 Areas	4 Vehicle groupings	51
Cluster/rotation, mean (SD)	1.8 (1.1)	3.0 (2.0)	25.1 (12.3)	19.2 (9.5)	7.6 (5.1)	4.3 (6.9)
Rotation interval	1 mo	1 mo	2 mo	8 wk	8 wk	
Start date (all in 2004)	July 22	October 28	September 9	August 17	November 17	

Abbreviations: ALS, advanced life support; BLS, basic life support; EMS, emergency medical services; NA, not available.
*In a single-tier system, emergency medical technicians and paramedics typically staff the same responding vehicle and respond to all emergency medical dispatches. In a 2-tier system, the first tier (BLS) is composed of emergency medical technicians who respond to all emergency medical dispatches. The second tier (ALS) is composed of paramedics and is reserved for more serious conditions including cardiac arrest. Typically BLS personnel arrive first at the scene although dispatch is often simultaneous.
†At any time, half of the study vehicles were assigned to load-distributing band cardiopulmonary resuscitation compression and the other half to manual compression.
‡Witnessed found in ventricular fibrillation.

Figure. Flow of Participants in Trial



CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; LDB, load-distributing band.
*Cost and the inconvenience of carrying the LDB-CPR device to episodes at which it would not be assigned dictated the use of cluster randomization with crossover. Within a given site, half of the clusters were randomized to the control (manual CPR) and half to the intervention (LDB-CPR) with subsequent alternation between the intervention and the control.
†Some patients had more than 1 exclusion.

clinical investigator. As prespecified in the study protocol, the data and safety monitoring board was to review safety and interim progress when approximately one third and two thirds of patients had been enrolled.

Population

Adults with out-of-hospital cardiac arrest who received attempted resuscitation by a participating EMS agency were enrolled unless an exclusion criterion was present (FIGURE). Patients treated by EMS subsequently determined to meet exclusion criteria were excluded from the analysis.

A primary comparison population, patients who were in cardiac arrest at the time of EMS arrival and whose cardiac arrest was considered to be of cardiac origin, was chosen a priori as the population most likely to benefit from chest compressions. Cardiac etiology was determined by the site study coordinator or investigator based on the EMS report forms and hospital records. Early in the enrollment, study adherence (application of the LDB-CPR device based on out-of-hospital report) was very low at site D when the advanced life support unit arrived before the study unit. Arrival of an advanced life support unit 90 seconds or longer before the study unit was added as a site-specific exclusion from the primary comparison population.

Study Protocol and Intervention

The device used in this study is approved by the US Food and Drug Administration and is the size of a half backboard, weighs 15.8 kg, and operates for longer than 60 minutes on battery power. To use the device, the patient's upper body clothing is removed, and the patient is placed supine on the backboard. An 8-inch wide LDB anchored behind the backboard is wrapped circumferentially around the patient's chest and is closed anteriorly with Velcro. The device automatically adjusts the length of the belt so that it fits snugly across the chest. Device-regulated, repetitive shortening of the belt squeezes the thoracic cavity, generating arterial circulation. Belt lengthening enables passive decompression of the chest. The device provides compressions at a rate of 80/min configured as 15 compressions with a 3-second pause for ventilations or continuous chest compressions without any ventilatory pause.

During a run-in period ranging from 0.7 to 2.8 months, EMS personnel integrated the automated device into out-of-hospital care. Initial training of EMS personnel included hands-on skill practice using the device with a mannequin and a video presentation with rationale for the LDB-CPR device. Refresher training was not specified by design to best replicate real-world conditions and was highly variable during the study.

The protocol allowed 3 options for the resuscitation intervention. Initially all sites chose option 1, a "quick look (<6 seconds)" rhythm recording followed by circulatory effort with either the LDB-CPR device (as soon as ready) or manual compressions by randomized assignment. After approximately 2 minutes or 200 manual compressions, a rhythm assessment was performed.

Option 2 was immediate CPR with manual compressions regardless of randomization until the first shock assessment. Site C, the only EMS with a comprehensive quality-improvement effort to reduce pauses in chest compressions, changed its resuscitation intervention to option two 110 days after starting the study. The change was implemented after quality-improvement review identified prolonged time without compressions while deploying the LDB-CPR device.

Option 3 allowed analysis, and shock if appropriate, before beginning CPR. In all cases, after rhythm assessment and shock if indicated, additional necessary compressions were to be performed manually or with the

LDB-CPR device according to randomization. In all other aspects, sites followed their standard resuscitation protocol until the patient was declared dead or regained stable spontaneous circulation and was transported to and arrived at the emergency department.

End Points

The primary end point was defined as survival with spontaneous circulation 4 hours after the 911 call. This measure avoids inherent inconsistencies in site-to-site variations in the definition of "admittance to the hospital." Secondary end points included discharge from the hospital and cerebral performance category score at discharge from the hospital that was obtained from the hospital records.[21]

Data Collection

Data were collected from EMS reports, defibrillator recordings, a study questionnaire, and hospital records.[22] Study personnel reviewed the defibrillator's digital electrocardiographic recording when available; otherwise electrocardiographic paper strips were reviewed. In addition, an experienced arrhythmia research nurse at the data coordinating center reviewed initial electrocardiographic records. If that review resulted in a discrepancy, the principal investigators, masked to treatment assignment, categorized the initial rhythm. Data collected from the hospital record were primarily used to monitor for adverse effects of chest compression and for ascertaining end points.

Sample Size

For sample size calculation, patients were assumed to be independent, although the crossover within cluster potentially could be more efficient.[23] The 4-hour survival rate was assumed to be the average of the baseline admittance and discharge survival rates. Based on available data from participating sites, we estimated survival to 4 hours (primary outcome) in the manual CPR group to be 17.8%. Based on reported improvements in restoration of spontaneous circulation rates from a small observational study of the device, a 35% relative improvement was hypothesized (ie, an intervention group primary outcome rate of 24.0%).[24] Thus, the study required 1837 patients in the primary comparison group to achieve a power of 90% using a 2-sided test with a level of .05 (based on sequential monitoring, 2 interim looks, and an O'Brien-Fleming type boundary).[25] The design included the possibility of increasing the sample size based on the observed outcomes to that point.[26]

Statistical Analysis

Comparisons were made by intention-to-treat assignment. Logistic regression was applied using generalized linear mixed models with the robust sandwich estimator of the variance to compare the outcome of individual episodes between the 2 study groups.[27-30] Models were adjusted for covariates previously demonstrated to predict survival[31,32] as well as cluster (a source of nonindependence).

A single a priori subgroup analysis of the primary population was specified based on initial rhythm (asystole, ventricular fibrillation/ventricular tachycardia, pulseless electrical activity). In 6.1% (47/767) of participants, electrocardiographic rhythm was not available and the automated external defibrillator did not advise to shock. These were assumed to be asystole or pulseless electrical activity. Three of the 47 cases were assigned the rhythm observed at the next electrocardiographic analysis. In the remaining 44 cases, the initial rhythm was imputed based on factors that discriminated significantly between patients with initial rhythm of pulseless electrical activity and asystole.

Post hoc subgroup analyses evaluated whether the intervention effect differed by site or by the time since the site began enrolling patients. Interactions were tested using an interaction term between treatment group and the covariate of interest.

Analyses were conducted using SPSS version 12.0 (SPSS, Chicago, Ill) and R version 2.3 (R Foundation for Statistical Computing) statistical software. Unless explicitly stated, *P* values are unadjusted for covariates or clustering. For the primary and secondary end points, *P* values were generally adjusted; by protocol, the α level for the primary end point was set at .05.

RESULTS

The data and safety monitoring board met on March 11, 2005, and again on March 28, 2005, to review the results for 757 patients enrolled through January 31, 2005, and recommended suspension of enrollment until data for the 314 patients enrolled during February and March could be evaluated. Results prompted additional data collection, including estimates of chest compression duration in the first 5 minutes of the resuscitation effort, drugs administered prior to the patient arriving at the hospital, mode of in-hospital death, and other details indicating lung, heart, or cerebral damage. On June 27, 2005, the steering committee reviewed these expanded data and recommended that the trial be halted.

There were 51 clusters, and the average number of episodes per cluster per rotation interval ranged from 1.8 to 25 (Table 1). The number of patient episodes enrolled at sites varied from 120 to 391. There were a total of 1377 episodes, of which 373 in the manual CPR group and 394 in the LDB-CPR group were eligible for study enrollment (Figure).

Demographic features, cardiac arrest circumstances, and treatment characteristics were generally similar between the treatment groups. Among primary cases, patients in the LDB-CPR group were more likely to receive epinephrine ($P=.03$) and have longer time intervals to first shock (for patients found in ventricular fibrillation/ventricular tachycardia) ($P=.001$), termination of resuscitative effort ($P=.01$), and hospital transport ($P=.01$) (TABLE 2). In the LDB-CPR group, the device was applied during the resuscitation to 83.8% of the primary cases, 73.5% of noncardiac cause cases,

Table 2. Episode Characteristics by Primary Case Status and Treatment Group*

	Nonprimary Case		Primary Case	
	Manual CPR (n = 144)	LDB-CPR (n = 160)	Manual CPR (n = 373)	LDB-CPR (n = 394)
Status				
Unwitnessed or unknown	51 (35.4)	65 (40.6)	192 (51.5)	219 (55.6)
Witnessed by bystander	36 (25.0)	36 (22.5)	181 (48.5)	175 (44.4)
Witnessed by EMS	57 (39.6)	59 (36.9)	NA	NA
CPR performed by bystander	26 (18.1)	23 (14.4)	132 (35.4)	127 (32.2)
Public location	30 (20.8)	34 (21.3)	79 (21.2)	69 (17.5)
Age, mean (SD), y	61.3 (18.9)	58.8 (18.3)	66.2 (15.2)	66.6 (15.6)
Men	95 (66.0)	106 (66.3)	245 (65.7)	252 (64.0)
Body type†				
Thin	22 (15.3)	17 (10.6)	33 (8.8)	56 (14.2)
Normal	46 (31.9)	55 (34.4)	133 (35.7)	157 (39.8)
Obese	22 (15.3)	39 (24.4)	84 (22.5)	87 (22.1)
Morbidly obese	4 (2.8)	6 (3.8)	9 (2.4)	17 (4.3)
Not reported‡	50 (34.7)	43 (26.9)	114 (30.6)	77 (19.5)
Rhythm				
VF/Pulseless VT	27 (18.8)	28 (17.5)	119 (31.9)	122 (31.0)
Pulseless electrical activity	58 (40.3)	54 (33.8)	94 (25.2)	79 (20.1)
Asystole	52 (36.1)	69 (43.1)	148 (39.7)	164 (41.6)
Uncertain	7 (4.9)	9 (5.6)	12 (3.2)	29 (7.4)
Time from 911 call, mean (SD), min				
First vehicle	5.9 (2.7)	5.8 (2.5)	5.7 (2.1)	5.6 (2.1)
Study vehicle	8.1 (6.4)	7.5 (4.2)	6.8 (3.2)	6.7 (2.7)
Advanced life support vehicle	8.6 (4.9)	8.7 (4.9)	8.0 (4.2)	8.1 (4.7)
EMS personnel performed CPR	14.8 (15.3)	12.2 (8.5)	7.8 (2.7)	7.9 (2.8)
LDB-CPR compressions				
Total	NA	95 (59.3)	NA	323 (82.0)
Time from 911 call, mean (SD), min	NA	14.7 (8.2)	NA	11.9 (4.5)
Time from 911 call to initial rhythm assessment, mean (SD), min	15.1 (15.0)	12.8 (8.2)	8.9 (2.9)	8.9 (3.0)
Time from 911 call to first shock for initial rhythm of VF/VT, mean (SD), min§	23.4 (28.1)	16.6 (9.9)	9.7 (3.1)	11.8 (6.1)
Proportion of the first 5 min on electrocardiogram with compressions, mean (SD) [No. of patients]	0.67 (0.25) [60]	0.60 (0.22) [57]	0.60 (0.20) [167]	0.59 (0.21) [203]
Advanced airway placed	123 (85.4)	129 (80.6)	310 (83.1)	342 (86.8)
Time from 911 call, mean (SD), min	19.2 (13.8)	18.1 (9.2)	15.4 (6.2)	14.9 (6.3)
Intravenous line inserted	122 (84.7)	143 (89.4)	319 (85.5)	342 (86.8)
Time from 911 call, mean (SD), min	18.1 (13.3)	16.8 (7.1)	15.5 (6.0)	15.9 (5.9)
Epinephrine administered‖	112 (77.8)	118 (78.1)	265 (82.8)	283 (89.1)
Dose, mean (SD), mg	3.8 (2.1)	3.9 (2.6)	4.0 (2.3)	3.9 (2.5)
Vasopressin administered	12 (8.3)	16 (10.0)	62 (16.6)	76 (19.3)
Dose, mean (SD), U	36.8 (11.3)	40.0 (0)	40.0 (0)	40.0 (0)
Bicarbonate administered	41 (28.5)	40 (25.0)	148 (39.7)	138 (35.0)
Intravenous administration or drip, mean (SD), mEq	70.3 (26.3)	64.7 (26.8)	66.4 (26.7)	67.3 (44.7)
Died at scene	36 (25.0)	49 (30.6)	130 (34.9)	133 (33.8)
Time from 911 call, mean (SD), min¶	36.8 (13.2)	34.0 (12.6)	33.9 (10.7)	37.5 (11.7)
Transported to hospital	108 (75.0)	111 (69.4)	243 (65.1)	261 (66.2)
Time from 911 call to time EMS began transport, mean (SD), min¶	36.7 (17.8)	35.5 (12.4)	32.0 (10.6)	34.9 (11.0)
Hypothermia therapy				
Prior to hospital arrival	3 (2.2)	3 (1.9)	3 (0.9)	7 (1.8)
In hospital	13 (9.0)	9 (5.6)	19 (5.1)	23 (5.6)

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; LDB, load-distributing band; NA, not applicable; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Values are expressed as number (percentage) unless otherwise indicated. All comparisons $P>.05$ except for certain comparisons among the primary cases as indicated.

†Body type was estimated by the paramedics treating the patient.

‡$P<.001$ (expected difference because device belt could not accommodate very thin or very obese persons).

§$P = .001$.

‖$P = .03$.

¶$P = .01$.

Table 3. Outcome by Treatment Group Overall and by Rhythm Subgroup Among Primary Comparison Population*

	VF/Pulseless VT		Pulseless Electrical Activity		Asystole		All Primary Cases†	
	Manual CPR (n = 119)	LDB-CPR (n = 122)	Manual CPR (n = 100)	LDB-CPR (n = 98)	Manual CPR (n = 154)	LDB-CPR (n = 174)	Manual CPR (n = 373)	LDB-CPR (n = 394)
Survived ≥4 h after 911 call	49 (41.2)	53 (43.4)	27 (27.0)	21 (21.4)	16 (10.4)	30 (17.2)	92 (24.7)	104 (26.4)
Died at scene	27 (22.7)	20 (16.4)	30 (30.0)	28 (28.6)	73 (47.4)	85 (48.9)	130 (34.9)	133 (33.8)
Died in emergency department	44 (37.0)	49 (40.2)	44 (44.0)	49 (50.0)	66 (42.9)	61 (35.1)	14 (41.3)	159 (40.4)
Died in hospital	21 (17.6)	36 (29.5)	17 (17.0)	18 (18.4)	14 (9.1)	25 (14.4)	52 (13.9)	79 (20.1)
Discharged alive from hospital	27 (22.7)	17 (13.9)	9 (9.0)	3 (3.1)	1 (0.6)	3 (1.7)	37 (9.9)	23 (5.8)
CPC score								
1, Conscious and alert	23 (19.3)	5 (4.1)	2 (2.0)	0	0	1 (0.6)	25 (6.7)	6 (1.5)
2, Conscious	2 (1.7)	5 (4.1)	0	1 (1.0)	1 (0.6)	0	3 (0.8)	6 (1.5)
3, Dependent	2 (1.7)	6 (5.0)	3 (3.1)	0	0	1 (0.6)	5 (1.3)	7 (1.8)
4, Unconscious	0	0	2 (2.0)	0	0	1 (0.6)	2 (0.5)	1 (0.3)
5, Circulatory death	92 (77.3)	105 (86.8)	91 (92.9)	95 (99.0)	153 (99.4)	171 (98.3)	336 (90.6)	371 (94.9)

Abbreviations: CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; LDB, load-distributing band; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Values are expressed as number (percentage).
†Neurological data were incomplete for 5 survivors.

and 52.5% of cases for which cardiac arrest occurred after EMS arrival. Among primary study patients, the mean (SD) time from 911 call to first use of the LDB-CPR device was 11.9 (4.5) minutes with a median of 10.9 minutes.

There was no significant difference in survival at 4 hours after the 911 call between the manual CPR group and the automated LDB-CPR group overall (N = 1071; 29.5% vs 28.5%; $P = .74$) or among the primary study population (n = 767; 24.7% vs 26.4%; $P = .62$). Survival to hospital discharge was lower in the LDB-CPR group among primary episodes (5.8% vs 9.9% [$P = .04$]; adjusted for covariates and clustering, $P = .06$), but similar among the nonprimary cases (10.6% vs 11.9%; $P = .72$). Excluding 5 survivors with incomplete neurological data, survival with a cerebral performance category score of 1 or 2 was recorded in 7.5% (28/371) of patients in the manual CPR group compared with 3.1% (12/391) in the LDB-CPR group ($P = .006$).

The survival effect of the LDB-CPR device differed, but not significantly ($P = .37$), according to initial rhythm of ventricular fibrillation, pulseless electrical activity, or asystole. In contrast to the ventricular fibrillation and pulseless electrical activity subgroups, outcomes trended better in the LDB-CPR group in the asystole subgroup for 4-hour survival (17.2% vs 10.4%) and hospital discharge (1.7% vs 0.6%) (TABLE 3).

Table 4. Logistic Regression of Survival to Hospital Discharge*

	Adjusted for Clustering			
	Univariable OR (95% CI)†	*P* Value	Multivariable OR (95% CI)†	*P* Value
Age per y	0.97 (0.96-0.99)	.002	0.98 (0.96-0.99)	.01
PEA to VF	0.28 (0.14-0.55)	<.001	0.36 (0.17-0.75)	<.001
Asystole to VF	0.05 (0.02-0.15)	<.001	0.09 (0.03-0.28)	<.001
Witnessed	5.30 (2.80-10.20)	<.001	2.40 (1.20-4.90)	.02
Site C	3.70 (2.10-6.50)	<.001	3.70 (2.00-7.00)	<.001
Response time of first vehicle/min	0.72 (0.60-0.86)	<.001	0.70 (0.58-0.85)	<.001
Public location	4.00 (2.30-6.90)	<.001	1.80 (0.97-3.40)	.06
LDB-CPR treatment group	0.57 (0.33-0.99)	.045	0.56 (0.31-1.00)	.06

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; LDB, load-distributing band; OR, odds ratio; PEA, pulseless electrical activity; VF, ventricular fibrillation.
*Variables considered but not significant in the models: univariable: days from site start (OR, 1.00 [95% CI, 0.99-1.00]; $P = .27$ [adjusted for clustering]); before December 28 (OR, 1.50 [95% CI, 0.86-2.50]; $P = .16$ [adjusted for clustering]); men (OR, 1.40 [95% CI, 0.79-2.70]; $P = .23$ [adjusted for clustering]); CPR performed by a bystander (OR, 1.40 [95% CI, 0.82-2.50]; $P = .21$ [adjusted for clustering]); response time of advanced life support vehicle (OR, 0.94 [95% CI, 0.87-1.02]; $P = .15$ [adjusted for clustering]). Interactions considered: treatment group × days from site start, $P = .84$; treatment group × site C, $P = .12$; treatment group × rhythm (with imputed rhythm values), $P = .37$.
†The ORs higher than 1 indicate a higher likelihood of survival and conversely, eg, the odds of survival decrease by 0.98 for each year of age, decrease by 0.36 if found in PEA than in VF, etc.

The results of the logistic regression analysis of hospital survival for the primary comparison cases are shown in TABLE 4. Traditional risk factors for unsuccessful resuscitation (older age, unwitnessed collapse, longer response time, nonpublic location, and initial rhythm of asystole or pulseless electrical activity) were confirmed. The association between hospital survival and treatment group did not differ over time from the start of the study at each site ($P = .84$ for interaction, adjusted for other covariates and clustering).

As expected from historical rates, survival was significantly better in site C compared with other sites (Table 4 and TABLE 5). However, the association between survival and treatment group did not differ significantly at site C compared with the other sites ($P = .12$ for interaction, adjusted for other covariates and clustering; Table 4). Both before and after the December 28 protocol change, EMS personnel at site C had higher protocol compliance and used the LDB-CPR device earlier in the resuscitative effort

than EMS personnel at the other sites (Table 5).

A post hoc multivariable analysis, which focused on patients who were treated relatively quickly after their cardiac arrest (witnessed primary cases found in ventricular fibrillation or pulseless electrical activity), indicated that as first vehicle response time shortened, patients in the manual CPR group were increasingly more likely to survive to hospital discharge compared with patients in the LDB-CPR group (interaction $P = .06$). At 6.6 minutes of response time, the model indicated the treatment groups would have the same survival.

Mode of death in the hospital was similar between the treatment groups. Approximately 35% died within 48 hours from a presumed cardiac cause.

COMMENT

In this trial comparing manual CPR with automated LDB-CPR, interim results prompted early termination as recommended by the data and safety monitoring board. Although 4-hour survival was similar between treatment groups among primary cardiac arrest episodes, hospital discharge survival was lower in the LDB-CPR group (5.8% vs 9.9%) as was survival with intact neurological status.

Evidence indicates that increased blood flow during CPR should translate to a higher likelihood of successful resuscitation.[2] The LDB-CPR device evaluated in this study produces greater circulation than manual CPR in animal models of cardiac arrest.[16,17] In observational human studies of the device, most but not all investigators have indicated greater likelihood of return of spontaneous circulation compared with historical controls, with 1 study demonstrating better survival to hospital discharge.[24,33,34] The results of the current randomized study were not expected and there is no obvious explanation.

One potential explanation is that patients in the manual CPR group benefitted from a Hawthorne effect such that manual CPR quality initially exceeded standard practice.[35] Conversely, there could have been a "learning curve" for use of the device with performance expected to improve over time. However, during the last 2 months, survival to hospital discharge for primary cases was 8.1% for manual CPR and 5.0% for LDB-CPR, findings similar to those from the initial months

Table 5. Comparison of Site C With Other 4 Sites for Primary Cases*

	Other Sites			Site C		
	Manual CPR (n = 307)	LDB-CPR (n = 329)	*P* Value for Site*	Manual CPR (n = 66)	LDB-CPR (n = 65)	*P* Value for Treatment Group†
Witnessed cardiac arrest	151 (49.2)	152 (46.2)	.13	30 (45.5)	23 (35.4)	.25
Age, mean (SD), y	65.9 (15.1)	66.7 (15.5)	.57	67.7 (15.6)	66.5 (16.0)	.87
VF/VT	97 (31.8)	101 (31.4)	.78	22 (33.3)	21 (32.3)	.87
Time from 911 call, mean (SD), min						
First EMS vehicle	5.9 (2.2)	5.7 (2.1)	<.001	4.9 (1.2)	5.0 (1.6)	.93
Advanced life support vehicle	7.9 (4.4)	8.0 (4.8)	.22	8.4 (3.4)	8.5 (3.9)	.88
First shock for VF/VT	9.8 (3.2)	12.0 (6.6)	.33	9.6 (2.8)	10.6 (2.7)	.05
Termination of resuscitative effort	34.7 (10.3)	38.2 (10.6)	.08	32.1 (11.3)	35.4 (14.2)	.03
Transported to hospital	31.4 (10.5)	34.4 (10.4)	.001	36.9 (10.2)	39.1 (14.6)	.09
LDB-CPR compressions attempted						
Before December 28 (Option 1 for site C)‡		150 (82.4)	.01§		27 (93.1)	.76§
After December 28 (Option 2 for site C)‖		118 (80.3)			35 (97.2)	
Time from 911 call to LDB-CPR compressions, mean (SD), min						
Before December 28 (Option 1 for site C)‡		11.6 (4.3)	<.001§		9.0 (2.1)	.009
After December 28 (Option 2 for site C)‖		13.1 (5.0)			10.9 (3.1)	
Survived ≥4 h after 911 call	68 (22.1)	82 (24.9)	.006	24 (36.4)	22 (33.8)	.55
Discharged alive from hospital	20 (6.5)	16 (4.9)	<.001	17 (25.8)	7 (10.8)	.04
CPC score						
1, Conscious and alert	14 (4.6)	5 (1.5)	.003¶	11 (16.9)	1 (1.5)	.008¶
2, Conscious	3 (1.0)	4 (1.2)		0	2 (3.1)	
3, Dependent	1 (0.3)	3 (0.9)		4 (6.2)	4 (6.2)	
4, Unconscious	1 (0.3)	1 (0.3)		1 (1.5)	0	
5, Circulatory death	278 (93.8)	313 (96.0)		49 (75.4)	58 (89.2)	

Abbreviations: CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; LDB, load-distributing band; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Values are expressed as number (percentage) unless otherwise indicated.
†*P* values are unadjusted. The model consisted of a variable (constant) plus site plus treatment group plus site × treatment group (identity or log-linear link) unless otherwise indicated. No interaction terms were significant.
‡Option 1 defined as rhythm recording followed by circulatory effort with either the LDB-CPR device or manual CPR.
§The model consisted of a variable (constant) plus site plus date (before and after December 28) plus site × date (before and after December 28).
‖Option 2 defined as immediate CPR with manual compressions regardless of randomization until the first shock assessment.
¶CPC scores 1 and 2 vs 3, 4, and 5.

of the study (11.7% and 8.0%, respectively).

Another possible explanation for the outcomes is that deployment time for the LDB-CPR device was prolonged. Mean time to first shock in primary cases with initial rhythm of ventricular fibrillation occurred 2.1 minutes later in the LDB-CPR group. While device deployment time was not measured directly, site C applied the device earlier and more frequently than the other sites and yet showed greater relative hazard for the intervention (Table 5).

Another implementation-based explanation is enrollment bias. Enthusiasm for the automated LDB-CPR device could have motivated EMS personnel to enroll patients who usually would have been declared dead on arrival. This may have occurred in a few cases because 21 more primary patients were enrolled in the LDB-CPR group compared with the manual CPR group. However, almost all long-term survivors were among patients whose initial rhythm was ventricular fibrillation, pulseless ventricular tachycardia, or pulseless electrical activity, and for whom enrollment and baseline characteristics were comparable between the 2 study groups. Moreover, the adverse intervention relationship was seen among patients presenting with ventricular fibrillation, a group that would routinely receive resuscitation and for whom enrollment bias was unlikely.

Other potential explanations for our findings may be related to the direct physiological effects of the automated device. Medications administered with superior blood flow generated by the device might exceed therapeutic thresholds and instead be toxic. However, we are unaware of evidence for such an effect. An additional consideration involves the manner in which blood flow is generated (ie, 80 compressions/min with the LDB-CPR device vs manual CPR rates of ≥100 compressions/min). There may be an as-yet unmapped relationship between time, flow, and reperfusion injury when early low blood flow may generate less reperfusion injury.[36,37] There is also the possibility that chest compressions by the LDB-CPR device may cause direct physical damage to the cardiopulmonary system, although review of hospital records to monitor for adverse events did not overtly identify this possibility.[38]

In addition, there is a 1 in 40 chance that the adverse survival outcome could have occurred under the null hypothesis of no treatment effect. In this regard, the possibility of unequal risk in the groups randomized at site C should be considered. That site accounted for 40% of the survivors, and survival in its manual CPR group was substantially greater than in previous years.

The effect of LDB-CPR compression may have differed depending on the presenting rhythm or time from collapse to resuscitation effort. Patients with asystole, potentially most consistent with untreated and longer arrest duration, appeared to benefit from the LDB-CPR compression whereas those with ventricular fibrillation or pulseless electrical activity appeared to experience harm. In a post hoc multivariable analysis of witnessed primary cases found in ventricular fibrillation or pulseless electrical activity, shorter response times favored the manual CPR group, while the model indicated the treatment groups would have the same survival when the response time reached 6.6 minutes ($P = .06$ for interaction). To some extent, this finding may be interpreted as consistent with other reports of observational human studies that have evaluated this LDB-CPR device.[24] These relationships and their underlying mechanisms require additional investigation.

Just as poor adherence dilutes the observed effect of a beneficial treatment, it also dilutes the effect of a harmful treatment. Thus, the observed differences between site C and the other sites are compatible with the overall impression that this implementation of mechanical CPR with the LDB-CPR device may be harmful. The differences are also compatible with the concept that the magnitude of harm may depend on the capabilities of the EMS system.

This study has several limitations. The LDB-CPR device was implemented at various stages of resuscitation, a flexibility designed to minimize CPR interruptions. A protocol requiring device implementation at a particular point of care might produce different results. For example, device application in apparently late stages of arrest (the asystole subgroup) appeared to be modestly beneficial. Although each site conducted a run-in phase with the device, more intensive training or a longer run-in phase may have produced different results. The study evaluated the proportion of time with CPR during the first 5 minutes of EMS resuscitation, but did not evaluate the "quality" of manual CPR (ie, rate, depth, recoil) or how manual and LDB-CPR compression differed later in the course of resuscitation. Because of adverse trends in safety outcomes, the study was terminated prior to complete enrollment. Although stopping the study for statistical futility was not part of the prespecified monitoring plan, the conditional power to detect the hypothesized difference in the primary outcome was only 0.55 at the time of study termination.

CONCLUSION

As implemented in this study, the use of an automated LDB-CPR device for resuscitation from out-of-hospital cardiac arrest appeared to result in lower survival and worse neurological outcomes than traditional manual CPR. Device design and implementation strategies may need further preclinical evaluation.

The results of this study underscore the complexity of resuscitation from out-of-hospital cardiac arrest. Further research is required to understand the interaction of manual or assisted chest compressions with other aspects of resuscitation such as the phase of the arrest,[39] drug choice and dose, timing of defibrillation, and treat-

ments such as hypothermia and coronary reperfusion.

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Study concept and design: Hallstrom, Rea, Sayre, Christenson, Anton, Mosesso, Van Ottingham, Cobb.
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REFERENCES

1. Stiell I, Nichol G, Wells G, et al. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation*. 2003;108:1939-1944.
2. Ewy GA. Cardiocerebral resuscitation: the new cardiopulmonary resuscitation. *Circulation*. 2005;111:2134-2142.
3. Gallagher EJ, Lombardi G, Gennis P. Effectiveness of bystander cardiopulmonary resuscitiation and survival following out-of-hospital cardiac arrest. *JAMA*. 1995;274:1922-1925.
4. Niemann JT. Cardiopulmonary resuscitation. *N Engl J Med*. 1992;327:1075-1080.
5. Yu T, Weil MH, Tang W, et al. Adverse outcomes of interrupted precordial compression during automated defibrillation. *Circulation*. 2002;106:368-372.
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;105:645-649.
7. Steen S, Liao Q, Pierre L, Paskevicius A, Sjoberg T. The critical importance of minimal delay between chest compressions and subsequent defibrillation: a haemodynamic explanation. *Resuscitation*. 2003;58:249-258.
8. Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. *JAMA*. 1999;281:1182-1188.
9. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA*. 2003;289:1389-1395.
10. Huseyin TS, Matthews AJ, Wills P, O'Neill VM. Improving the effectiveness of continuous closed chest compressions: an exploratory study. *Resuscitation*. 2002;54:57-62.
11. Ochoa FJ, Ramalle-Gomara E, Lisa V, Saralegui I. The effect of rescuer fatigue on the quality of chest compressions. *Resuscitation*. 1998;37:149-152.
12. Hightower D, Thomas SH, Stone CK, Dunn K, March JA. Decay in quality of closed-chest compressions over time. *Ann Emerg Med*. 1995;26:300-303.
13. Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *JAMA*. 2005;293:305-310.
14. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA*. 2005;293:299-304.
15. Timmerman S, Cardoso LF, Ramires JA. Improved hemodynamics with a novel chest compression device during treatment of in-hospital cardiac arrest. *Prehosp Emerg Care*. 2003;7:162.
16. Halperin HR, Paradis NA, Omato JP. Improved hemodynamics with a novel chest compression device during a porcine model of cardiac arrest. *Circulation*. 2002;106:538.
17. Ikeno F, Kaneda H, Hongo Y, et al. Augmentation of tissue perfusion by a novel compression device increases neurologically intact survival in a porcine model of prolonged cardiac arrest. *Resuscitation*. 2006;68:109-118.
18. Hallstrom AP, Paradis NA. Pre-randomization and de-randomization in emergency medical research: new names and rigorous criteria for old methods. *Resuscitation*. 2005;65:65-69.
19. Protection of Human Subjects, 45 CFR §46.116 (1997).
20. Protection of Human Subjects, 21 CFR §50.23 (1979).
21. Herlitz J, Ekstrom L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Prognosis among survivors of prehospital cardiac arrest. *Ann Emerg Med*. 1995;25:58-63.
22. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385-3397.
23. Connelly LB. Balancing the number and size of sites: an economic approach to the optimal design of cluster samples. *Control Clin Trials*. 2003;24:544-559.
24. Casner M, Andersen D, Isaacs SM. The impact of a new CPR assist device on rate of return of spontaneous circulation in out-of-hospital cardiac arrest. *Prehosp Emerg Care*. 2005;9:61-67.
25. *East Version 3.0: Software for the Design, Simulation and Interim Monitoring of Flexible Clinical Trials User Manual*. Cambridge, Mass: Cytel Software Corp; 2003.
26. Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. *Stat Med*. 2004;23:1023-1038.
27. Venables WN, Ripley BD. *Modern Applied Statistics With S*. 4th ed. New York, NY: Springer Publishing Co; 2002.
28. Rogers WH. Regression standard errors in clustered samples. *Stata Tech Bull Rep*. 1993;3:88-94.
29. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56:645-646.
30. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data*. Cambridge, Mass: MIT Press; 2002.
31. Vukmir RB. Survival and outcome from prehospital cardiac arrest. http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijrdm/vol4n1/survival.xml. Accessibility verified May 15, 2006.
32. Rea TD, Eisenberg MS, Becker LJ, Murray JA, Hearne T. Temporal trends in sudden cardiac arrest: a 25-year emergency medical services perspective. *Circulation*. 2003;107:2780-2785.
33. Lairet J, Lee M. A comparison of standard manual cardiopulmonary resuscitation versus the AutoPulse mechanical cardiopulmonary resuscitation device. *Ann Emerg Med*. 2005;46:S114.
34. Ornato J. An emergency medical services system resuscitation strategy: using AutoPulse™ as the primary method for delivering chest compressions improves survival from out-of-hospital cardiac arrest (late-breaking trial presentation). Presented at: American Heart Association Resuscitation Science Symposium; November 11-12, 2005; Dallas, Tex.
35. Campbell JP, Maxey VA, Watson WA. Hawthorne effect: implications for prehospital research. *Ann Emerg Med*. 1995;26:590-594.
36. Anderson T, Vanden Hoek TL. Preconditioning and the oxidants of sudden death. *Curr Opin Crit Care*. 2003;9:194-198.
37. Blackstone E, Morrison M, Roth MB. H2S induces a suspended animation-like state in mice. *Science*. 2005;308:518.
38. Hart AP, Azar VJ, Hart KR, Stephens BG. Autopsy artifact created by the Revivant AutoPulse resuscitation device. *J Forensic Sci*. 2005;50:164-168.
39. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA*. 2002;288:3035-3038.

