Comparison of Standard Cardiopulmonary Resuscitation Versus the Combination of Active Compression-Decompression Cardiopulmonary Resuscitation and an Inspiratory Impedance Threshold Device for Out-of-Hospital Cardiac Arrest

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Background—Active compression-decompression (ACD) CPR combined with an inspiratory impedance threshold device (ITD) improves vital organ blood flow during cardiac arrest. This study compared survival rates with ACD+ITD CPR versus standard manual CPR (S-CPR).

Methods and Results—A prospective, controlled trial was performed in Mainz, Germany, in which a 2-tiered emergency response included early defibrillation. Patients with out-of-hospital arrest of presumed cardiac pathogenesis were sequentially randomized to ACD+ITD CPR or S-CPR by the advanced life support team after intubation. Rescuers learned which method of CPR to use at the start of each work shift. The primary end point was 1-hour survival after a witnessed arrest. With ACD+ITD CPR (n=103), return of spontaneous circulation and 1- and 24-hour survival rates were 55%, 51%, and 37% versus 37%, 32%, and 22% with S-CPR (n=107) (P=0.016, 0.006, and 0.033, respectively). One- and 24-hour survival rates in witnessed arrests were 55% and 41% with ACD+ITD CPR versus 33% and 23% in control subjects (P=0.011 and 0.019), respectively. One- and 24-hour survival rates in patients with a witnessed arrest in ventricular fibrillation were 68% and 58% after ACD+ITD CPR versus 27% and 23% after S-CPR (P=0.002 and 0.009), respectively. Patients randomized ≥10 minutes after the call for help to the ACD+ITD CPR had a 3 times higher 1-hour survival rate than control subjects (P=0.002). Hospital discharge rates were 18% after ACD+ITD CPR versus 13% in control subjects (P=0.41). In witnessed arrests, overall neurological function trended higher with ACD+ITD CPR versus control subjects (P=0.07).

Conclusions—Compared with S-CPR, ACD+ITD CPR significantly improved short-term survival rates for patients with out-of-hospital cardiac arrest. Additional studies are needed to evaluate potential long-term benefits of ACD+ITD CPR. **(*Circulation*. 2003;108:2201-2205.)**

Key Words: cardiac arrest ■ cardiopulmonary resuscitation ■ treatment

Profound vital organ hypoperfusion contributes significantly to the dismal survival rates observed with manual CPR after cardiac arrest. Recent data demonstrate that the combination of active compression-decompression (ACD) CPR and an inspiratory impedance threshold valve device (ITD) (ACD+ITD CPR) results in a >3-fold increase in blood flow to the heart and brain compared with standard (S-) CPR.[1–5] The ACD device is a hand-held device with a suction cup to attach to the chest and a gauge to help determine the forces needed for effective compression and decompression. By itself, the ACD CPR device creates a vacuum within the thorax with each chest wall decompression, but much of the potential hemodynamic benefit of this vacuum is lost by the influx of inspiratory gas. The ITD is a small, 35-mL, device that fits on a face mask or an endotracheal tube. The pressure-sensitive valves within the ITD impede the influx of inspiratory gas during chest wall decompression, thereby augmenting the amplitude and duration of the vacuum within the thorax. This vacuum draws more venous blood back into the heart, resulting in increased cardiac preload, followed by improved cardiac output and vital

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organ perfusion. Building on recent animal and clinical studies,[1–5] this study compared survival rates after treatment with manual S-CPR versus ACD+ITD CPR in patients with out-of-hospital cardiac arrest.

Methods

This prospective, randomized, controlled trial in Mainz, Germany, was approved by the Ethics Committee of the Regional Medical Council of Rhineland-Palatinate, Germany, on September 15, 1997. The Mainz emergency medical services system serves ≈200 000 inhabitants. It is 2 tiered, with basic life support, early defibrillation, and a paramedic in the first tier and a physician-staffed mobile intensive care unit with full advanced cardiac life support in the second tier. It has been described previously.[6]

Patients were randomized to receive S-CPR or ACD+ITD CPR. The ITD (ResQValve, Advanced Circulatory Systems, Inc) selectively prevents inspiration during the decompression phase of CPR, except when the rescuer ventilates the patient.[4,5] ACD CPR was performed with a CardioPump (Ambu International) to compress and actively decompress the chest.[7,8]

Before starting the study, 105 emergency medical services (EMS) personnel (active paramedics, emergency medical technicians, and physicians) were trained to perform ACD+ITD CPR and retrained in S-CPR. Retraining sessions for both techniques were conducted every 3 months for the first year using written and hands-on training aids. Each training session lasted 2 hours. Equal time was spent teaching the new technique and reviewing S-CPR. During subsequent years, the frequency of retraining was reduced to an annual basis.

All patients were treated according to American Heart Association and European Resuscitation Council Guidelines (basic life support, defibrillation, standard-dose epinephrine every 3 to 5 minutes).[7,9] Before randomization, S-CPR and early defibrillation, if indicated, were performed on all patients. After the arrival of the mobile intensive care unit and verification of cardiac arrest by the emergency physician on scene, patients were intubated and randomized to ACD+ITD CPR or S-CPR. Randomization was performed by use of a case-by-case computer-generated randomization list. Rescuers learned which method to use at the beginning of each work shift. After intubation, compressions and ventilation were performed asynchronously. Compression and decompression were performed with ACD+ITD CPR or S-CPR at 100 times/min and ventilations at a rate of 10 to 12 breaths/min. To prevent rescuer fatigue, rescuers rotated performance of CPR every 4 to 5 minutes. EMS personnel were instructed to provide CPR for a minimum of 30 minutes or until a pulse returned. The quality of CPR was monitored by the investigators at the scene (B.B.W., D.K.M., M.F.K., H.T.) in ≈25% of cases to ensure proper performance of both methods of CPR. Feedback was provided as needed to the rescue personnel related to their performance of each CPR technique during and after each cardiac arrest.

Only patients with out-of-hospital cardiac arrest of presumed cardiac etiology who were hand-bag ventilated via an endotracheal tube were enrolled.[10] Exclusion criteria were age <18 years, traumatic injuries, known terminal illness (eg, metastatic cancer), "do not resuscitate" (DNR) orders, circumstances precluding implementation of either method of CPR, known prolonged time (>15 minutes) between collapse and initiation of any CPR, when family members requested discontinuation of resuscitation, and when endotracheal intubation was not possible.

The primary study end point was 1-hour survival after hospital admission in witnessed cardiac arrest. This end point was determined a priori and was used to determine the overall study sample size. Additional major clinical study end points, analyzed for all enrolled patients, were return of spontaneous circulation (ROSC), 24-hour survival, survival to hospital discharge, and neurological recovery. Further subgroup analyses were based on the presenting rhythm and whether the arrests were witnessed. Data were collected according to Utstein Guidelines and Glasgow-Pittsburgh Cerebral and Overall Performance Category (CPC and OPC) neurological scoring systems.[10] Both the CPC and OPC scoring systems have been well described. In brief, a CPC=1 means normal cerebral function, 2 means mild to moderate impairment, 3 means severe impairment, and 4 means the patient is comatose or in a vegetative state. The OPC scoring system is similar, but includes measurements of both cognitive and functional processes. Complication rates and adverse events were analyzed as well.

An external and independent Data and Safety Monitoring Board was established before the study was started. For ethical reasons, an interim analysis was performed to assess adverse events and the likelihood of demonstrating efficacy at the planned enrollment size.

Independent statistical analyses were performed by a coauthor (D.A.). Data were analyzed on an intention-to-treat basis. A total of 210 eligible patients in cardiac arrest were estimated to provide an 80% power of identifying a 50% difference in 1-hour survival at a significance level of 0.05 by χ^2 test. Sample size calculations were based on a previous trial in Mainz in which the hospital admission rate was 33% with S-CPR.[6]

Results were analyzed by χ^2, Fisher's exact test, unpaired 2-tailed *t* test, and logistic regression. All probability values were for 2-sided test, and a value of $P<0.05$ was considered statistically significant. The treatment groups and subgroups were compared, with respect to possible covariates, to determine which had to be taken into account in the end-point analyses. The odds ratios and 95% CIs for the primary and secondary end points were calculated by the Cochran-Mantel-Haenszel method. In addition, the secondary survival end points were combined with the primary end point into a single survival analysis. The differences between the 2 CPR techniques for the single survival analysis were evaluated by Wilcoxon's and log rank tests. For comparison of the adverse events, Fisher's exact test was used. The statistical software package SAS (SAS Institute Inc, SAS/STAT, Version 8, Cary, NC, 1999) was used for data analyses.

Results

This study was performed between January 1999 and March 2002 in Mainz, Germany. There was a 5-month pilot phase to introduce and implement the protocol and new CPR technique. During the study period, there were 322 patients in cardiac arrest. Of these, 77 patients were not entered into the study for the following reasons: traumatic etiology (n=16), ROSC before randomization (n=24; of these, 19 were in ventricular fibrillation [VF] and 5 had pulseless electrical activity), in-hospital cardiac arrest (n=10), interval between witnessed collapse and start of CPR >15 minutes (n=10), could not be intubated with an endotracheal tube (n=3), <18 years old (n=2), and presence of DNR orders (n=12). Of the 24 patients with a ROSC before randomization, 14 of 19 patients in VF and 2 of 5 patients in pulseless electrical activity were discharged from the hospital, and all had a CPC score of 1 or 2. Of the 245 patients randomized by the mobile intensive care unit staff, 35 were subsequently excluded from the study for the following reasons: ROSC without intubation (n=4, all in VF), in-hospital cardiac arrest (n=2), interval between arrest and start of CPR determined to be >15 minutes (n=14), presence of DNR orders (n=8), prevention of CPR treatment because of limited access (n=1), and known or presumed noncardiac etiology (n=6). There were 2 randomization errors, 1 per group; neither had a ROSC.

Characteristics of the 210 patients enrolled and included in the analysis are shown in Table 1. The groups did not differ significantly in terms of age, gender, weight, witnessed arrest, bystander CPR, initial rhythm, response time intervals for all categories described, duration of CPR performed, and total epinephrine dosage.

TABLE 1. Patient Characteristics

Variable	Standard CPR (n=107)	ACD+ITD CPR (n=103)	P
Age, y, mean±SD (range)	66.8±16.5 (18–99)	67.2±17.2 (21–100)	0.74
Male gender, n (%)	63/107 (59)	67/103 (65)	0.44
Estimated weight, kg, mean±SD (range)	78.7±7.4 (45–160)	79.7±14.0 (50–120)	0.65
Arrest not witnessed, n (%)	32/107 (30)	21/103 (20)	0.26
Emergency call to arrival of first EMS responder to scene, min, mean±SD (range)	6.0±2.7 (1–13)	5.9±2.4 (1–13)	0.8
Emergency call to arrival of MICU, min, mean±SD (range)	9.4±4.9 (3–30)	9.6±3.7 (1–21)	0.8
Bystander CPR, n (%)	25/94 (27)	26/91 (29)	0.89
Initial rhythm			0.4
V-fib/pulseless V-tach, n (%)	38/107 (36)	46/103 (45)	
PEA, n (%)	29/107 (27)	33/103 (32)	
Asystole, n (%)	40/107 (37)	24/103 (23)	
CPR duration,* minutes, mean±SD (range)	34.0±13.8 (20–105)	35.0±9.0 (15–59)	0.6
Total epinephrine administered,* mg±SD (range)	10.0±7.7 (3–43)	11.5±5.8 (4–26)	0.4

MICU indicates mobile intensive care unit; V-fib, ventricular fibrillation; V-tach, ventricular tachycardia; and PEA, pulseless electrical activity.

*In those patients not achieving ROSC.

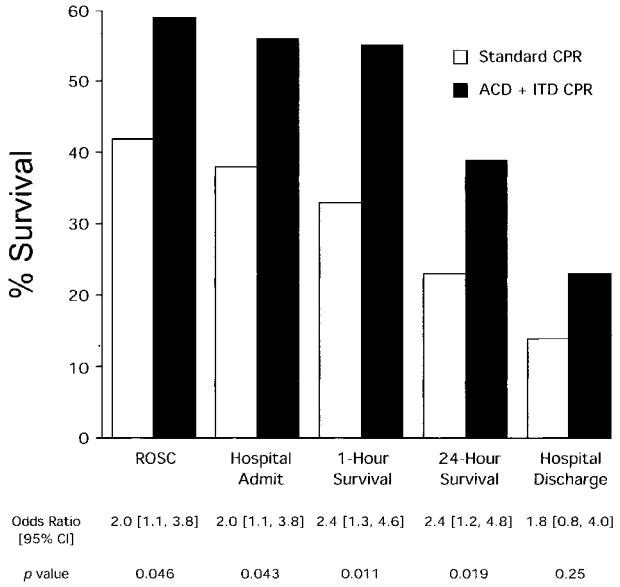
The presence of a palpable pulse during CPR, ROSC, 1-hour survival, 24-hour survival, hospital discharge rates, and neurological outcomes are shown in Table 2. There was a statistically significant increase in 1-hour and 24-hour survival rates for all patients enrolled in the study who were treated with ACD+ITD CPR. The percentage of patients who lived to hospital discharge trended higher with ACD+ITD CPR but was not significantly different between groups (13% for S-CPR and 18% for ACD+ITD CPR). However, using the Wilcoxon and log rank tests of the different end points to calculate a single survival rate outcome, there was a significant increase in survival rates for all eligible cases ($P=0.008$ and $P=0.032$) and witnessed cases ($P=0.015$ and $P=0.025$), respectively.

The primary end point for the study was 1-hour survival after a witnessed cardiac arrest in which the collapse to start of CPR was <15 minutes. Nearly twice as many witnessed arrest patients survived for 1 hour and 24 hours with ACD+ITD CPR versus control subjects (Figure). The odds ratios (ORs) and CIs for 1- and 24-hour survival rates in the ACD+ITD CPR versus control subjects were 2.4 (1.28, 4.62) and 2.4 (1.21, 4.83), respectively. Hospital discharge rates were 15% versus 23% for patients with a witnessed arrest (P=NS). The numbers of patients with a normal neurological recovery (CPC=1) were not statistically different between groups: 4 of 75 (5%) with S-CPR versus 8 of 82 (10%) with ACD+ITD CPR ($P=0.4$; OR, 1.9; CI, 0.6, 6.6), respectively. A total of 9 of 75 survivors (12%) in the control group versus 14 of 82 (17%) in the ACD+ITD CPR group had a CPC of 1 or 2 ($P=0.5$; OR, 1.6; CI, 0.6, 3.7). There was a trend toward improved neurological and physical function with ACD+ITD CPR: 4 of 75 (5%) in the control group versus 12 of 82 (15%) in the ACD+ITD CPR group had an OPC score of 1 or 2 ($P=0.07$; OR, 3.0; CI, 0.98, 9.8).

In subgroup analyses based on rhythm, the 1- and 24-hour survival rates for patients in VF, comparing S-CPR versus ACD+ITD CPR, were 32% versus 65% and 26% versus 54% ($P=0.002$; OR, 4.0; CI, 1.6, 0.7 and $P=0.01$; OR, 3.2; CI, 1.3,

TABLE 2. Outcome for All Patients

Outcome	Standard CPR (n=107), n (%)	ACD+ITD CPR (n=103), n (%)	Odds Ratio (95% CI)	P
Pulse with CPR	74 (69)	88 (85)	2.5	0.008
ROSC	40 (37)	57 (55)	2.0 (1.1, 3.5)	0.016
1-Hour survival	34 (32)	53 (51)	2.1 (1.2, 3.9)	0.006
24-Hour survival	24 (22)	38 (37)	1.9 (1.1, 3.6)	0.033
Hospital discharge	14 (13)	19 (18)	1.3 (0.6, 3.0)	0.41
Neurological score at hospital discharge				
CPC=1	5/14 (36)	8/19 (42)	1.3 (0.3, 5.6)	1.0
CPC=1 or 2	11/14 (79)	14/19 (74)	0.8 (0.15, 4.0)	1.0
OPC=1	1/14 (7)	1/19 (5)	0.7 (0.04, 13.2)	1.0
OPC=1 or 2	6/14 (43)	12/19 (63)	2.3 (0.5, 9.4)	0.3



Comparison of survival outcomes of 2 CPR groups with calculated probability values, ORs, and 95% CIs for patients with a witnessed cardiac arrest. One-hour survival after a witnessed cardiac arrest was the primary study end point.

8.0, respectively). For patients with a witnessed arrest in VF, the benefits of ACD+ITD CPR were even more striking: 27% of the control subjects lived for 1 hour versus 68% in the new treatment group ($P=0.002$; OR, 5.7; CI, 2.07, 15.9). For patients not in VF, use of ACD+ITD CPR resulted in a nonsignificant increase in survival rates: the 1-hour survival rate for all cases was 32% with S-CPR and 40% for ACD+ITD CPR ($P=0.39$; OR, 1.4; CI, 0.7, 2.8).

Analysis was performed to determine whether there was a difference in 1-hour survival rates for patients in whom the call for help to mobile intensive care unit arrival time was ≥10 minutes. Patients whose arrest was witnessed by either the first- or second-tier EMS responders (n=25) were excluded from this analysis. ACD+ITD CPR more than tripled the chances for survival (44%) when initiated late compared with S-CPR (14%) ($P=0.005$; OR, 4.9; CI, 1.6, 14.4). This benefit was observed for all initial heart rhythms. The number of patients with a CPC score of 1 or 2 was similar in the ACD+ITD CPR group, regardless of the time that the new devices were applied.

Potential adverse events and complications rates are shown in Table 3. Except for superficial ecchymosis at the contact site between the ACD CPR device and the chest, there were no statistically significant differences in complications between groups. The ACD CPR device could not be used in 5 patients (5%) secondary to poor suction. There were no device failures.

TABLE 3. Adverse Events and Complications From CPR (All Eligible Cases)

Adverse Event	Standard CPR (n=107), n (%)	ACD+ITD CPR (n=103), n (%)	*P*
Chest fractures (rib and sternal)	14 (13)	18 (17)	0.44
Ecchymosis	2 (2)	51 (50)	0.001
Pulmonary edema	0 (0)	3 (4)	0.12
Vomiting during CPR	8 (7)	12 (12)	0.35
Poor suction with ACD CPR device	NA	5 (5)	NA
ITD device failure	NA	0	NA
ACD CPR device failure	NA	0	NA

NA indicates not applicable.

Discussion

Consistent with earlier animal and human studies,[1–5,11,12] the results from this first clinical comparison of S-CPR versus ACD+ITD CPR demonstrated that there was a significant improvement in ROSC and 1- and 24-hour survival rates for all patients in the new treatment group. The improvement in short-term survival was notable in patients with a witnessed arrest; however, the short-term impact on survival with ACD+ITD CPR was most striking in patients with VF who were not resuscitated by 3 sequential DC shocks before randomization. In this subgroup, more than twice as many patients lived for >24 hours after treatment with ACD+ITD CPR and subsequent defibrillation (26%) versus control subjects (54%). In addition, use of ACD+ITD CPR more than tripled 1-hour survival rates compared with control subjects in patients for whom the response time was ≥10 minutes after the call for help. This time-related increase in short-term survival was observed regardless of the presenting rhythm. These findings demonstrate that the "window of opportunity" for successful resuscitation can be extended by enhancing circulation with ACD+ITD CPR. Although this study was not statistically powered or primarily designed to evaluate neurological function or hospital discharge rates, use of ACD+ITD CPR resulted in a significant overall short-term survival benefit and a strong trend toward improvement in neurological outcome. Larger studies will be needed to evaluate the long-term potential benefits of ACD+ITD CPR.

A previous study in Mainz found equivalent survival rates when comparing ACD CPR alone versus S-CPR.[6] Historically in Mainz, the hospital admission and discharge rates with S-CPR were 33% and 14%, respectively.[6] By contrast, in the present Mainz study, use of ACD+ITD CPR resulted in a significant increase in survival rates. Taken together, these studies provide strong physiological support of the value of enhancing cardiopulmonary and cerebral circulation with the ITD. It is possible that the ITD and not ACD CPR may have provided most of the observed short-term survival benefit in this study. Additional studies are under way to test this hypothesis.

The importance of training in the performance of S- and ACD CPR has been previously described .[7,8] Rescuers were required to undergo initial and refresher training in ACD+ITD CPR and S-CPR 5 times in the first 2 years of this study. Moreover, the physicians on scene provided rescuers with feedback to ensure that both methods of CPR were performed correctly. The importance of compressing to the correct depth, actively decompressing, and rotating performance of CPR frequently to avoid fatigue was emphasized during training of ACD+ITD CPR. We believe this contributed to the success of this technique. There were no significant increases in significant adverse events when study groups were compared. In no case did rescue personnel fail to remove the ITD after ROSC.

This study has limitations. First, it could not be blinded. This may have affected the level of enthusiasm of the rescuers, biasing them in favor of the new technique. However, survival rates in the control group were identical to those of historical control subjects,[6] and there were only 2 randomization errors. To further avoid bias, EMS personnel did not learn about the study results until after publication, and no investigators were involved in any way with the in-hospital care of any patients. Second, high-dose epinephrine was used in some patients after lower doses failed. Previous reports have shown that ACD CPR alone is not effective with high-dose epinephrine.[13] Third, there was not a statistically significant difference in hospital discharge rates. The study was powered only to detect a difference in 1-hour survival rates. Given the 13% hospital discharge rate in the control subjects, enrollment of >1000 patients would have been needed to detect a 50% increase in hospital discharge rates. Survivors in both groups died in the hospital for multiple reasons, making it difficult to fully evaluate the long-term potential of the new technology. However, recent advances in postresuscitation care after successful initial resuscitation efforts suggest that concurrent administration of other therapies, especially induced hypothermia after cardiac arrest,[14,15] may further improve the long-term survival rates and neurological outcomes. Without short-term survival, there is no chance to evaluate these potential longer-term therapies. Fourth, to ensure consistent CPR quality, ACD+ITD CPR was performed relatively late in the sequence of resuscitation efforts. Thus, the present study design may have underestimated the potential of this new approach, because delays decrease survival rates. Because the ITD can be used in patients ventilated with a face mask or an endotracheal tube,[16] we speculate that a more rapid initiation of ACD+ITD CPR could increase survival rates further. Finally, by chance, there were greater numbers of unwitnessed cardiac arrest and patients not in VF in the S-CPR group. Patients with a witnessed arrest or an initial rhythm of VF have more favorable outcomes after cardiac arrest. Nonetheless, those patients who did have a witnessed arrest or VF had a markedly higher short-term survival rate when randomized to the ACD+ITD CPR group.

Although ACD+ITD CPR is not a panacea, it can significantly strengthen a traditionally weak link in the chain of survival after cardiac arrest. The benefits of ACD+ITD CPR in the present study provide further evidence that "priming the pump" increases the chance for successful defibrillation.[17] The present study demonstrates that use of ACD+ITD CPR also increases the chances for successful defibrillation. The benefits of ACD+ITD CPR are further supported by a recent prospective randomized and blinded French study in which addition of an ITD in patients already receiving ACD CPR resulted in a 50% increase in 24-hour survival rates after out-of-hospital cardiac arrest.[18] On the basis of the results from the present study, we conclude that performance of ACD+ITD CPR should be encouraged to increase resuscitation rates for all patients in cardiac arrest. The present study demonstrated that use of ACD+ITD CPR improved short-term survival rates, but additional studies are needed to evaluate the potential to improve long-term survival with this new technique.

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