Clinical evaluation of an inspiratory impedance threshold device during standard cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest*

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Objective: **To determine whether an impedance threshold device, designed to enhance circulation, would increase acute resuscitation rates for patients in cardiac arrest receiving conventional manual cardiopulmonary resuscitation.**

Design: **Prospective, randomized, double-blind, intention-to-treat.**

Setting: **Out-of-hospital trial conducted in the Milwaukee, WI, emergency medical services system.**

Patients: **Adults in cardiac arrest of presumed cardiac etiology.**

Interventions: **On arrival of advanced life support, patients were treated with standard cardiopulmonary resuscitation combined with either an active or a sham impedance threshold device.**

Measurements and Main Results: **We measured safety and efficacy of the impedance threshold device; the primary end point was intensive care unit admission. Statistical analyses performed included the chi-square test and multivariate regression analysis. One hundred sixteen patients were treated with a sham impedance threshold device, and 114 patients were treated with an active impedance threshold device. Overall intensive care unit admission rates were 17% with the sham device vs. 25% in the active impedance threshold device ($p = .13$; odds ratio, 1.64; 95% confidence interval, 0.87, 3.10). Patients in the subgroup presenting with pulseless electrical activity had intensive care unit admission and 24-hr survival rates of 20% and 12% in sham (n = 25) vs. 52% and 30% in active impedance threshold device groups (n = 27) ($p = .018$, odds ratio, 4.31; 95% confidence interval, 1.28, 14.5, and $p = .12$, odds ratio, 3.09; 95% confidence interval, 0.74, 13.0, respectively). A *post hoc* analysis of patients with pulseless electrical activity at any time during the cardiac arrest revealed that intensive care unit and 24-hr survival rates were 20% and 11% in the sham (n = 56) vs. 41% and 27% in the active impedance threshold device groups (n = 49) ($p = .018$, odds ratio, 2.82; 95% confidence interval, 1.19, 6.67, and $p = .037$, odds ratio, 3.01; 95% confidence interval, 1.07, 8.96, respectively). There were no statistically significant differences in outcomes for patients presenting in ventricular fibrillation and asystole. Adverse event and complication rates were also similar.**

Conclusions: **During this first clinical trial of the impedance threshold device during standard cardiopulmonary resuscitation, use of the new device more than doubled short-term survival rates in patients presenting with pulseless electrical activity. A larger clinical trial is underway to determine the potential longer term benefits of the impedance threshold device in cardiac arrest. (Crit Care Med 2005; 33:734–740)**

KEY WORDS: cardiopulmonary resuscitation; impedance threshold device; sudden death; heart arrest; survival; pulseless electrical activity

An inspiratory impedance threshold device (ITD) has recently been demonstrated to enhance vital organ perfusion and neurologically intact survival rates in animals in cardiac arrest during standard cardiopulmonary resuscitation (CPR) (1–4). The ITD is a small, 35-mL device that can attach to a variety of airway adjuncts, including a facemask and endotracheal tube (Fig. 1). By selectively impeding inspiratory gas exchange during the decompression phase of CPR, the ITD lowers intrathoracic pressure and enhances venous blood return to the heart. Building on animal studies, we tested the hypothesis that the ITD would increase short-term survival rates in patients receiving CPR for treatment of out-of-hospital cardiac arrest, even when applied late in resuscitation.

MATERIALS AND METHODS

This prospective, double-blind, randomized clinical trial was performed in the Milwaukee County (Wisconsin) emergency medical services (EMS) system, according to federal regulations that permit an exception from informed consent for emergency research (21 §CFR Part 50.24) and a U.S. Food and Drug Administration approved investigational device exemption. The Human Research Review Committee at the Medical College of Wiscon-

***See also p. 898.**

From the Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI (TPA, RGP); Advanced Circulatory Systems, Eden Prairie, MN (TAP, KGL); and the Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN (KGL).

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Dr. Lurie is co-inventor of the impedance threshold device and the active compression decompression cardiopulmonary resuscitation device and founded a company, Advanced Circulatory Systems, to further develop this technology. Ms. Provo is the director of clinical trials for Advanced Circulatory Systems. Dr. Aufderheide is a paid consultant to Medtronic Physio-Control and has received research funding from GE Marquette Medical Systems as well as NHLBI SBIR Phase II and Phase II Continuation grant monies. He perceives no direct conflicts of interest in the presentation of data in this manuscript. Dr. Pirrallo owns shares of Zoll Medical Corp. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official views of the NIH National Heart, Lung and Blood Institute.

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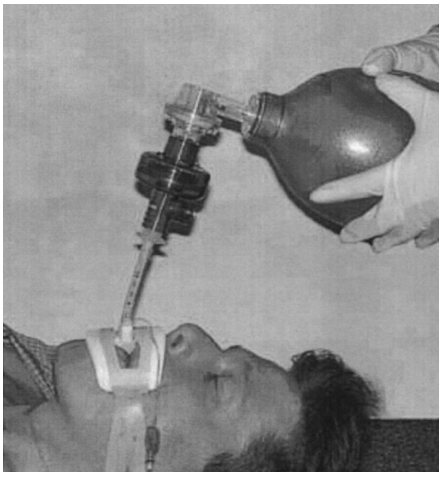

Figure 1. Impedance threshold device (ResQ-Valve) inserted between the bag-mask ventilator and the endotracheal tube.

sin and seven additional institutional review boards representing 13 paramedic-receiving hospitals in the Milwaukee area approved the study. Informed consent for continued participation in the trial was attempted for all subjects surviving to hospital admission.

A description of the two-tiered Milwaukee County EMS system has been previously reported (5).

During the study period, all adult patients treated with CPR for an out-of-hospital cardiac arrest of presumed cardiac etiology were sequentially randomized to receive either an active or a sham ITD (Advanced Circulatory Systems, Eden Prairie, MN) on arrival of the second-tier advanced life support (ALS) personnel. Rescuers were instructed to initially place the ITD on a facemask and then move it to the endotracheal tube once the subject was successfully intubated. The Milwaukee County EMS system provides emergency cardiac care based on American Heart Association guidelines (6). Before the onset of the study, EMS personnel were given CPR refresher training and were observed in the classroom to ventilate and perform CPR according to those guidelines.

Inclusion criteria included a) adults (known or presumed to be ≥21 yrs) who had resuscitation attempted and who presented with cardiac arrest of presumed cardiac etiology; and b) successful endotracheal intubation or successful resuscitation during facemask ventilation with an ITD. Exclusion criteria included a) subjects known or presumed to be <21 yrs; b) subjects with suspected noncardiac arrest etiology; c) subjects unable to be hand-bag ventilated, intubated with an endotracheal tube, or only intubated with a Combitube; d) subjects with preexisting do not resuscitate orders; and e) subjects who were resuscitated before application of the ITD. These inclusion and exclusion criteria are consistent with the Utstein guidelines on resuscitation (7). The only treatment difference between the two groups was that the experimental group (active ITD) received inspiratory impedance during CPR, whereas the control group (sham ITD) did not. Rescuers were instructed to remove the ITD if the subject had a return of spontaneous circulation.

All subjects were randomized by the first ALS unit to the scene. Block randomization and blinding were performed as follows. Each ambulance company received a supply of ten devices (five actives and five shams) to be used in a computer-generated, randomized order, which were then replaced with new randomized devices following use. Each device was packaged separately, in a sealed and nontranslucent package, preventing any possible means to identify whether the package contained an active or sham device. Active devices provided inspiratory impedance by not permitting inspiratory air flow unless a pressure of greater than -16 cm H_2O was generated at the patient port. Sham devices were manufactured to appear externally identical but offered no inspiratory impedance, essentially functioning as a hollow conduit to ventilatory gases. Neither device impeded positive pressure ventilation or exhalation. In this way, rescuers and investigators were blinded to the type of device (active or sham) being used.

The primary end point of this intention-to-treat study was survival to intensive care unit (ICU) admission. *A priori*, it was determined that additional statistical analyses would be performed to determine the effect of the ITD on short-term survival outcomes based on whether the arrest was witnessed. It was also determined *a priori* that a subgroup analysis based on rhythm (ventricular fibrillation/pulseless ventricular tachycardia, asystole, and pulseless electrical activity) and correlation with rates of return of spontaneous circulation, ICU admission, 1-hr survival, 24-hr survival, and survival to hospital discharge would be performed. Adverse events (pulmonary edema and device failure) and complications from CPR (vomiting) were also prospectively identified and monitored. Outcome data were obtained from EMS records, hospital charts, patient/family interview, and publicly available data sources. Data were collected and analyzed following the Utstein guidelines for cardiac arrest research (7). Neurologic function, as determined by the Cerebral Performance Category scoring system from 1 to 5 (1, normal; 2, mild cognitive impairment; 3, major cognitive impairment; 4, severe neurologic impairment; 5, comatose), was evaluated in the patients who survived to hospital discharge and again at 30 days postarrest (7). One-year neurologic function was evaluated using a quality of life questionnaire adapted for cardiac arrest survivors based on the Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire (8).

The results of hospital chest radiographs and postmortem exams, when available, were reviewed. Data and adverse events were reviewed by an independent statistician, Clinical Events Committee, and Data and Safety Monitoring Board (DSMB). The chi-square test was used for comparison of survival rates between groups. Before the onset of the study, a power analysis predicted enrollment of a total of 276 patients per arm to detect a 50% increase in ICU admission rates from an *a priori* anticipated rate of 22% in the control group to 33% in the experimental treatment group. Based on the anticipated ICU admission rates and therapeutic benefit, this planned sample size was sufficient to demonstrate statistical significance ($p < .05$) with a power of 0.8 using a two-tailed analysis.

Univariate and multivariate logistic regression analyses were used to determine the impact of additional variables on survival rates. The following variables were considered potential covariates/confounders in the comparison between active and sham ITD: age, gender, bystander CPR, witnessed arrest, time from 911 to arrival of first EMS unit, and time from 911 to arrival of ALS. An initial multivariate analysis was performed that evaluated the impact of all six covariates simultaneously. In view of the relatively few number of patients who survived to ICU admission, especially in the subgroups, there was a concern of overadjustment; therefore, backward elimination was used. In a backward elimination, the variable with the highest p value greater than a prescribed threshold value was eliminated. This process was repeated for the remaining covariates. A threshold value of .30 was chosen, unless the removal of the variable next in line for elimination produced a >2.5% reduction in the percent of concordant pairs in predicted and observed values. In this circumstance, concordance percent was a measure of model fit, which was, in the case of the multivariate regression analyses performed, between 60% and 70%.

RESULTS

A total of 230 subjects were enrolled over an 8-month period. A total of 116 subjects in the sham ITD group and 114 subjects in the active ITD group qualified for final inclusion in the study. There were no statistically significant differences in the clinical characteristics between the active and sham groups (Table 1).

During the study period, paramedics responded to 526 calls for presumed cardiac arrest. In 265 cases, a subject was not entered if he or she failed to meet *a priori* inclusion criteria as shown in Table

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Table 1. Subject characteristics

	Sham ITD (n = 116)	Active ITD (n = 114)	*p* Value
Age ± SD, yrs	66.5 ± 16.7	64.4 ± 15.4	.320
Males, n (%)	72 (62)	69 (61)	.892
Height ± SD, in.	67.6 ± 3.9	67.8 ± 3.7	.677
Weight ± SD, lb	176.2 ± 53.6	185.5 ± 52.8	.246
Witnessed arrest, n (%)	69 (60)	66 (58)	.894
Bystander CPR, n (%)	29/94 (31)	22/97 (23)	.252
Witnessed collapse to CPR time ± SD, mins	3.7 ± 4.3	4.3 ± 4.3	.409
EMS response ± SD, mins	4.7 ± 2.3	4.7 ± 2.9	.870
ALS response ± SD, mins	6.8 ± 3.6	6.8 ± 3.8	.980
911 time to ITD placement ± SD, mins	11.5 ± 5.3	12.9 ± 5.6	.093
EMS CPR duration ± SD, mins	31.9 ± 11.0	31.3 ± 12.0	.672
Presenting cardiac rhythm, n (%)			.640
Asystole	59 (51)	58 (51)	
V-fib/pulseless V-tach	31 (27)	28 (24)	
PEA	25 (21)	27 (24)	
Unknown	1 (1)	1 (1)	
PEA at any time, n (%)	56 (48)	49 (43)	.508

ITD, impedance threshold device; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ALS, advanced life support; V-fib, ventricular fibrillation; V-tach, ventricular tachycardia; PEA, pulseless electrical activity.

Table 2. Resuscitations not attempted with an impedance threshold device (ITD)

Reason	No.
Combitube in place prior to ITD	87
Age <21 yrs	41
Resuscitation not attempted (DOA)	39
Presumed noncardiac etiology	37
Preexisting DNR order	24
Failed to enroll[a]	12
Inability to intubate with cuffed ET	11
ROSC prior to ITD placement	11
Respiratory arrest only	2
Subject enrolled in another trial	1
Total	265

DOA, dead on arrival; DNR, do not resuscitate; ET, endotracheal tube; ROSC, return of spontaneous circulation.

[a]Protocol deviation.

2. After entry (and an ITD was used), a total of 31 subjects (15 active, 16 sham) were subsequently excluded from data analysis as they did not meet final inclusion criteria as shown in Table 3. In addition, investigators asked the DSMB to review 31 cases to determine whether a given patient should or should not be included in the study based on the *a priori* enrollment criteria. DSMB members were blinded to the treatment (device function) received. The DSMB recommended that 12 patients should not be included in the study (five active ITD patients, seven sham ITD cases), and these patients were subsequently excluded from the analysis as shown in Table 4.

ICU admission was the primary study end point. The ICU admission and 24-hr survival rates for all patients who met enrollment criteria were 17% and 12% with the sham device vs. 25% and 17% in the active ITD. The *p* values, odds ratio, 95% confidence intervals, and results of univariate regression analyses are shown in Table 5. Patients with a witnessed arrest who were treated with the active ITD (n = 66) had an ICU admission rate of 32% vs. 22% in the sham group (n = 69). The *p* value was .19, and odds ratio and confidence intervals were 1.68 (0.78, 3.63).

In patients presenting with pulseless electrical activity (PEA), 1-hr, ICU admission, and 24-hr survival rates were 20%, 20%, and 12% with the sham (n = 25) and 56%, 52%, and 30% with the active ITD (n = 27). The *p* values, odds ratios, and confidence intervals for results related to return of spontaneous circulation, ICU admission, and 24-hr survival rates are also shown in Table 5. Nearly half of all subjects had PEA at some point during their resuscitation; half presented with PEA and the other half developed PEA during the resuscitation effort. Using a *post hoc* analysis, there was a significant increase in ICU admission and 24-hr survival rates for patients with PEA who received an active vs. sham ITD (Table 5). In patients with PEA at any time during resuscitation, 1-hr, ICU admission, and 24-hr survival rates were 21%, 20%, and 11% with the sham (n = 56) vs. 43%, 41%, and 27% with the active ITD (n = 49; *p* = .018, .018, and .037, respectively; Fig. 2).

The ICU admission and 24-hr survival in patients presenting with ventricular fibrillation and pulseless ventricular tachycardia were 26% and 19% with the sham ITD (n = 31) vs. 32% and 32% with the active ITD (n = 28), respectively. The *p* values, odds ratios, and confidence intervals for these comparisons are shown in Table 5.

In this study, half the patients presented in an initial rhythm of asystole. The active ITD had no discernable beneficial effect in patients who presented in asystole.

Multivariate regression analyses were performed. The six covariates that were initially considered for these analyses were gender, age, presence of bystander CPR, witnessed arrest, time from 911 to first EMS response, and time from 911 to ALS response. Based on these analyses, the odds ratio (95% confidence interval) for the primary end point, ICU admission for all patients in cardiac arrest, was 1.99 (1.0, 4.0) with $p = .05$. However, due to concerns of overadjusting, especially with relatively low sample sizes, a further multivariate regression analysis with a backward elimination was performed as described in the Methods section. Based on those further analyses, the odds ratio (95% confidence interval) for the primary end point, ICU admission for all patients in cardiac arrest, was 1.9 (0.92, 3.5) with $p = .086$. When we used the backward elimination method for the multivariate analysis, the results of the univariate analysis and multivariate were similar to those described in Table 5. The multivariate analysis did not alter the *p* values related to ICU admission rates for all patients or subgroups based on heart rhythm.

The study was powered to evaluate the impact of the ITD on ICU admission rates. Too few patients survived to hospital discharge to make statistically meaningful comparisons about discharge rates or neurologic function given the small sample size. Neurologic function was normal (Cerebral Performance Category score = 1) at the time of hospital discharge and 30 days after arrest in one fourth of patients who survived in the sham ITD group and in three fifths of patients who survived in the active ITD group. Patients or their family members refused to (or did not) sign a postenrollment informed consent for hospital chart review or additional follow-up in five pa-

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Table 3. Cases receiving an impedance threshold device (ITD) but subsequently excluded from final data analysis

Reason	No. Active	No. Sham
Noncardiac etiology	5	2
Outcomes of cases excluded due to noncardiac etiology	2, no ROSC; 1, ROSC; 2, ICU	1, no ROSC; 1, 24 HrS
Unable to intubate with ET → Combitube	5	6
Unable to intubate with ET → facemask only	1	2
DNR order subsequently discovered	2	3
Respiratory arrest only[a]	1	1
Leaky or uncuffed ET tube	0	2
Enrolled previously	1	0
Total	15	16

ROSC, return of spontaneous circulation; ICU, survival to intensive care unit admission; 24 HrS, survival to 24 hrs; ET, endotracheal tube; DNR, do not resuscitate.

[a]Protocol deviation.

Table 4. Cases reviewed by the Data Safety and Monitoring Board for inclusion/exclusion

Decision	No. Active	No. Sham
Include case	8	11
Exclude due to likely noncardiac etiology	4	2
Outcomes of cases excluded due to noncardiac etiology	2, no ROSC; 1, ROSC; 1, ICU	1, no ROSC; 1, 24 HrS
Exclude due to DNR status	1	2
Exclude case due to leaky or uncuffed ET	0	2
Exclude case; ET pulled and Combitube inserted	0	1
Total	13	18

ROSC, return of spontaneous circulation; ICU, survival to intensive care unit admission; 24 HrS, survival to 24 hrs; DNR, do not resuscitate; ET, endotracheal tube.

Table 5. End point data for all patients and by cardiac rhythm

	Active, %	Sham, %	Odds Ratio (95% CI)	*p* Value
All Patients	n = 114	n = 116		
ROSC	37.7	31.9	1.29 (0.75, 2.23)	.355
ICU	25.4	17.2	1.64 (0.87, 3.10)	.13
24 HrS	16.7	12.1	1.46 (0.69, 3.07)	.32
PEA initially	n = 27	n = 25		
ROSC	59.3	36.0	2.59 (0.84, 7.93)	.097
ICU	51.9	20.0	4.31 (1.28, 14.5)	.018
24 HrS	29.6	12.0	3.09 (0.74, 13.0)	.123
PEA at any time	n = 49	n = 56		
ROSC	61.2	42.9	2.11 (0.96, 4.6)	.06
ICU	40.8	19.6	2.82 (1.19, 6.67)	.018
24 HrS	26.5	10.7	3.01 (1.07, 8.96)	.037
V-fib/V-tach initially	n = 28	n = 31		
ROSC	42.9	51.6	0.70 (0.25, 1.97)	.505
ICU	32.1	25.8	1.36 (0.44, 4.21)	.595
24 HrS	32.1	19.4	1.97 (0.60, 6.51)	.264
Asystole initially	n = 58	n = 59		
ROSC	24.1	20.3	1.25 (0.52, 2.99)	.62
ICU	8.6	11.9	0.70 (0.21, 2.35)	.57
24 HrS	1.7	8.5	0.19 (0.02, 1.67)	.10

CI, confidence intervals; ROSC, return of spontaneous circulation; ICU, survival to intensive care unit admission; 24 HrS, survival to 24 hours; PEA, pulseless electrical activity; V-fib, ventricular fibrillation; V-tach, ventricular tachycardia.

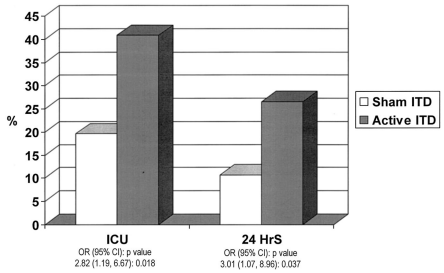

Figure 2. Outcomes for all patients in pulseless electrical activity at anytime during cardiac arrest (sham impedance threshold device [*ITD*] group, n = 56; active ITD group, n = 49). *24 HrS*, survival to 24 hrs; *CI*, confidence intervals; *ICU*, survival to intensive care unit admission; *OR*, odds ratio.

tients in the sham and two patients in the active ITD group. At the 1-yr follow up, data were available on all study participants: Those patients from whom we could not obtain consent earlier from family members had died. There were four survivors in the active ITD group and two survivors in the sham ITD group: All reported that their overall quality of life 1 yr after cardiac arrest was as good then as it had been before the arrest.

The adverse event and complication rates were similar between groups. In the entire group of patients receiving sham (n = 132) and active (n = 129) devices, the following adverse events were reported: a) pulmonary edema as evidenced by the ITD filling with fluid twice: two (1.5%) in the sham vs. one (<1%) in the active group; b) inability to ventilate: one (<1%) in the sham vs. none (0%) in the active group; and c) subcutaneous emphysema: none (0%) in the sham vs. one (<1%) in the active group. In the group of patients receiving a chest radiograph on arrival at the hospital (sham, n = 21; active, n = 29), the following adverse event was reported: pulmonary edema as evidenced by findings on the first chest radiograph obtained, six (28%) in the sham vs. eight (28%) in the active group. In addition, one patient receiving an active ITD was found to have evidence of pulmonary edema on postmortem exam. In the groups included in the final data analysis (sham, n = 116; active, n = 114), the following complication rates were reported: vomiting during ITD use, 14 (12%) in the sham vs. nine (8%) in the active group.

Enrollment in the study was discontinued prematurely. As recently described (9), subject enrollment was initially suspended to retrain all EMS personnel on the proper performance of CPR, based on data from a separate hemodynamic study that was performed in Milwaukee at the same time as the current clinical outcomes trial. The hemodynamic study demonstrated that patients were ventilated at maximal ventilation rates averaging 37 ± 4 breaths/min instead of the

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recommended 12–15 breaths/min before further training to comply with the guidelines (9). Enrollment was prematurely discontinued by the investigators and the sponsor in the present study for several reasons. First, the control group ICU admission rate was significantly lower than anticipated as *a priori* survival rates had included patients resuscitated by early defibrillation alone or by very short periods of CPR. On recalculation, a sample size of nearly 450 per arm would have been needed to observe a statistically significant increase in ICU admission rates from 17% to 25%. Second, to prevent hyperventilation, a timing device was needed to guide rescuers to ventilate at the proper rate; and third, rescuers were frequently observed to fail to allow the chest wall to fully recoil after each compression, as recommended in American Heart Association guidelines (6). Based on these observations, made during part of a hemodynamic study that overlapped in Milwaukee contemporaneously with the current clinical outcomes study, all EMS personnel were required to undergo a system-wide retraining of proper CPR technique. Special emphasis during the retraining was placed on the importance of preventing hyperventilation and allowing the chest to fully recoil after each compression. Each of the critical issues was readdressed, and plans for a new and larger clinical trial with an ITD that incorporates ventilation timing lights are underway.

DISCUSSION

In this first randomized, prospective, blinded trial evaluating use of an ITD in patients with out-of-hospital cardiac arrest, the active ITD more than doubled short-term survival rates for patients with an initial heart rhythm of PEA. Nearly half of the patients in this study had documented PEA at some time during their cardiac arrest. Using a *post hoc* analysis, 24-hr survival rates were 11% with the sham ITD and 27% with the active ITD for all patients in PEA at any time during cardiac arrest ($p = .037$). Although short-term survival rates were also higher in patients initially presenting with ventricular fibrillation and asystole, the number of patients enrolled at the time the study was terminated was too small to draw any statistically meaningful conclusions. Based on the current results, demonstrating an increase in ICU admission rates from 17% with the sham device to 25% with the active ITD ($p = .13$), more than 900 patients would be needed to adequately power a study to detect a statistically significant difference in ICU admission rates for all patients with the active ITD.

The results of this study demonstrate that the combination of standard CPR and the ITD significantly improved short-term survival rates for victims of cardiac arrest with PEA, a patient population previously shown to have a dismal outcome (10).

Previous investigations have demonstrated that in some cases of PEA there is evidence of spontaneous regular electrical activity that is associated with small increases in arterial blood pressure (11). A similar observation was made in a concurrent hemodynamic study focused on the effects of the ITD on blood pressure, which is the subject of a separate report. With pseudo-PEA there is an increase in arterial blood pressure associated with each cardiac depolarization, but the overall blood pressure is too low to be detected clinically by a pulse check. Building on these observations, the current results support the hypothesis that the ITD provides a novel means to increase circulation during CPR to a threshold level high enough to result in a palpable return of spontaneous circulation.

These new findings with the ITD and CPR are consistent with and support the findings of earlier studies demonstrating the benefits of the ITD with active compression decompression (ACD) CPR (12–14). In those studies, use of the ITD and ACD CPR significantly increased 24-hr survival rates (13, 14). In a blinded, prospective, randomized 400-patient trial with a sham vs. active ITD in patients undergoing ACD CPR, 24-hr survival rates were 44 of 200 (22%) in the sham vs. 64 of 200 (32%) in the active device groups ($p < .05$) (13). A similar survival benefit was observed in a second trial comparing standard CPR alone with ACD CPR plus an ITD, in which 24-hr survival rates were 22% with standard CPR alone and 37% with ACD CPR plus an ITD ($p = .03$) (14). An earlier study comparing ACD CPR with a sham vs. active ITD demonstrated that use of the active device resulted in significantly higher end-tidal carbon dioxide levels, higher coronary perfusion pressures, and nearly normal blood pressures (approximately 110/55 mm Hg), even after prolonged periods of time between arrest and use of the active ITD (12).

During this first clinical trial of the impedance threshold device during standard cardiopulmonary resuscitation, use of the new device more than doubled short-term survival rates in patients presenting with pulseless electrical activity.

The current study is also consistent with reports of good neurologic function in survivors following use of an active ITD (13, 14). For example, one of eight (12.5%) patients with a sham ITD vs. six of ten (60%) patients with an active ITD ($p = .06$) had neurologically intact survival following use of an ITD and ACD CPR (13). In another study, four of 75 (5%) in the standard CPR control group vs. 12 of 82 (15%) in the ITD plus ACD CPR group had a normal or near-normal overall neurologic function ($p = .07$; odds ratio, 3.0; confidence interval, 0.98, 9.8) following witnessed cardiac arrest (14). In the current study, four patients in the active ITD group and two patients in the sham ITD group were alive at the end of the year. All four patients in the active ITD group and one of the two patients in the control group reported that their overall satisfaction and happiness about their life were the same as before the cardiac arrest. The second patient in the control group reported a decrease in his quality of life compared with before the arrest. None of these studies has yet been designed from a statistical standpoint to adequately examine the potential neurologic benefits of the ITD.

From a mechanistic standpoint, these data support the hypothesis that survival after cardiac arrest is critically dependent on sufficient blood flow to the vital organs to allow for recovery of cardiac function and restoration of brain function. A doubling of blood flow to the myocardium has been reported by two separate groups of investigators in animal models of cardiac arrest (1, 2, 4), and an increase in blood flow to the brain has been ob-

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served in two separate studies using the ITD during CPR (1, 2). The current results support the hypothesis that the ITD provides a sufficient increase in circulation to double the likelihood of short-term survival in patients with PEA. As such, there appears to be a good correlation between the animal models (1–4, 15), the present study, and the European trials (12–14).

The ITD appears to have a satisfactory safety profile. There were no significant differences in adverse events or complication rates observed with the ITD in the current study compared with control group adverse event rates. A cracking (or opening) pressure of −16 cm H_2O was selected for this trial based on the observation in humans undergoing active compression decompression CPR that the maximum negative intrathoracic pressure generated during the chest wall recoil phase was approximately −12 mm Hg, approximately equivalent to −16 cm H_2O. With >750 cardiac arrest patients treated with an active ITD in the present study and several European trials (12–14), no clinically significant adverse effects have been observed.

A number of errors in the delivery of CPR were observed during the period of time that this clinical trial was conducted. Excessive ventilation rates were frequently observed, despite rigorous educational efforts to reduce them (9). Hyperventilation during CPR results in consistently positive intrathoracic pressures, preventing venous return to the heart, thereby markedly reducing coronary perfusion pressure and survival rates from cardiac arrest (9). Furthermore, a high incidence of incomplete chest wall recoil was also observed (16) and was subsequently shown in animals to further reduce coronary and cerebral perfusion pressures by the same mechanism (17, 18). These common errors in the delivery of CPR by professional rescuers are not unique to the Milwaukee County EMS system and may have significant implications for interpretation and design of clinical research trials and the training and practice of CPR. Nonetheless, despite these deficiencies in CPR technique, which have now been demonstrated to decrease the hemodynamic effectiveness of CPR in animals (9, 17, 19), use of the active ITD in this current study still had a beneficial effect on ICU admission rates, especially in subjects with PEA. This is particularly encouraging as the incidence of PEA in cardiac arrest populations appears to be increasing (20). Based on prior animal studies and studies with the combination of the ITD and active compression decompression CPR, where full chest wall recoil is ensured by a mechanical device, we speculate that improving the quality of CPR delivered at the scene of cardiac arrest will further enhance the benefits of ITD use.

This initial evaluation of the ITD in patients undergoing CPR has several limitations. First, the full potential value of the ITD is unknown with this investigation, in part because the study was terminated prematurely. Challenges associated with professional rescuer CPR performance were uncovered during the course of a concurrent hemodynamic study that temporally overlapped this survival study in the same study site (9, 16). We believe that excessive ventilation rates and incomplete chest wall recoil may have reduced hemodynamics and the likelihood for survival in both groups. To address this problem in future clinical studies, the investigators added ventilation timing assist lights to an improved ITD that flash 12 times per minute to help provide rescuers with the proper guidance on ventilation frequency and inspiratory duration. In addition, during the study rescuers were initially taught and then retaught to allow the chest to fully recoil after each compression, per American Heart Association Guidelines (6). These changes were made based on field observations and studies with manikins demonstrating that chest wall recoil remains incomplete unless the palm of the hand is lifted slightly but completely off the chest at the end of each decompression (16). These fundamental issues related to CPR performance resulted in the decision to terminate the present study, provide new tools to EMS personnel to improve CPR quality, and initiate a new and larger ITD study.

Another limitation is that the ITD was applied relatively late in the course of the resuscitation effort. The average time from arrest to ITD application was approximately 12 mins. We speculate that improved quality of CPR and earlier application of the ITD by basic life support personnel will further enhance survival rates after cardiac arrest. A third important limitation relates to the *a priori* statistical assumptions for ICU admission rates in the control group that significantly overestimated the actual ICU admission rates, in part because the *a priori* assumptions included data from patients resuscitated by early defibrillation alone with no or minimal periods of CPR. This observation has implications for the design of future clinical trials. Finally, hypothermia was not used in patients who survived to hospital admission. Hypothermia has been shown in some patient subgroups to improve outcomes after cardiac arrest and will be considered in future studies (21, 22).

CONCLUSION

Use of an ITD during CPR in patients with out-of-hospital cardiac arrest more than doubled short-term survival for patients with PEA. The study was designed to address the potential benefits of this technology in a sequential manner. As such, the potential long-term benefits of this technology, in terms of improved neurologically intact survival rates, have been demonstrated in animal models of cardiac arrest (3) but remain speculative in humans. Based on the positive results from this study, a larger clinical trial with the improved ITD is underway to evaluate long-term survival outcomes for all patients in cardiac arrest.

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