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ORIGINAL ARTICLE

A Trial of an Impedance Threshold Device in Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

The impedance threshold device (ITD) is designed to enhance venous return and cardiac output during cardiopulmonary resuscitation (CPR) by increasing the degree of negative intrathoracic pressure. Previous studies have suggested that the use of an ITD during CPR may improve survival rates after cardiac arrest.

METHODS

We compared the use of an active ITD with that of a sham ITD in patients with out-of-hospital cardiac arrest who underwent standard CPR at 10 sites in the United States and Canada. Patients, investigators, study coordinators, and all care providers were unaware of the treatment assignments. The primary outcome was survival to hospital discharge with satisfactory function (i.e., a score of ≤3 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating greater disability).

RESULTS

Of 8718 patients included in the analysis, 4345 were randomly assigned to treatment with a sham ITD and 4373 to treatment with an active device. A total of 260 patients (6.0%) in the sham-ITD group and 254 patients (5.8%) in the active-ITD group met the primary outcome (risk difference adjusted for sequential monitoring, −0.1 percentage points; 95% confidence interval, −1.1 to 0.8; P=0.71). There were also no significant differences in the secondary outcomes, including rates of return of spontaneous circulation on arrival at the emergency department, survival to hospital admission, and survival to hospital discharge.

CONCLUSIONS

Use of the ITD did not significantly improve survival with satisfactory function among patients with out-of-hospital cardiac arrest receiving standard CPR. (Funded by the National Heart, Lung, and Blood Institute and others; ROC PRIMED ClinicalTrials.gov number, NCT00394706.)

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Standard cardiopulmonary resuscitation (CPR), defined as manual chest compressions with rescue breathing, can be lifesaving but provides only a relatively small fraction of normal cardiac output, even when performed correctly.[1,2] One proposed strategy to augment cardiac output during CPR is the use of an impedance threshold device (ITD).[3-5]

The ITD is designed to enhance venous return and cardiac output during CPR by increasing the degree of negative intrathoracic pressure (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). This effect is achieved by preventing the passive inflow of air into the chest during chest recoil between chest compressions without impeding active ventilation. The ITD has been found to improve hemodynamics, the perfusion of vital organs, and neurologically intact survival in studies in animals.[3-5] The results of small, short-term clinical trials have suggested that the ITD can increase systolic blood pressure during resuscitation and improve short-term survival rates.[6-8] The 2005 American Heart Association guidelines gave a class IIa recommendation for use of the ITD to improve hemodynamic variables and the return of spontaneous circulation, although increased long-term survival rates had not been documented.[9] We therefore conducted a large, randomized trial to test whether standard CPR with the use of an active ITD, as compared with standard CPR with the use of a sham ITD, improves rates of hospital discharge with satisfactory function for adults with out-of-hospital cardiac arrest.

Methods

Study Setting and Design

We carried out a randomized comparison of the use of an active ITD with that of a sham ITD during standard CPR. This investigation was designed, reviewed, and implemented by the Resuscitation Outcomes Consortium (ROC) and was conducted concurrently with a companion study of early rhythm analysis versus later rhythm analysis, reported by Stiell et al. elsewhere in this issue of the *Journal*.[10] Most patients were enrolled simultaneously in both components of the ROC Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis (ROC PRIMED) trial: the active-ITD-versus-sham-ITD component and the early-analysis-versus-later-analysis component, although the eligibility criteria for the two components were slightly different. Details of the trial design and the relationship between the two studies can be found in the article by Stiell et al.,[10] in a previously published description of the trial methods,[11] and in the Supplementary Appendix.

The trial was supported by the National Heart, Lung, and Blood Institute; the National Institute of Neurological Disorders and Stroke; the Canadian Institutes of Health Research; and the Heart and Stroke Foundation of Canada. The manufacturer of the ITD, Advanced Circulatory Systems, supplied devices to the study network at a reduced price for the trial and provided nonbinding advice to the investigators about the design of the study before it was implemented. The authors vouch for the completeness and accuracy of the data and of all analyses and for the fidelity of the study to the trial protocol (available at NEJM.org).

Patient Population

All adults with nontraumatic, out-of-hospital cardiac arrest were eligible for enrollment if they were being treated with resuscitative efforts by emergency medical services (EMS) personnel who were participating in the ROC. Patients were excluded if they were incarcerated, were known to be pregnant, had do-not-attempt-resuscitation orders, had arrest due to exsanguinations or severe burns, had an existing tracheostomy, or were undergoing attempted resuscitation with the use of other mechanical CPR devices. This study qualified for exception from informed consent required for emergency research according to the U.S. Food and Drug Administration and Canadian Tri-Council Agreement regulations. The protocol was approved by local institutional review and research ethics boards.

Treatment Assignments

Patients were randomly assigned to undergo CPR that included either an active ITD or an identical-appearing sham ITD. Each device was packaged in a sealed plastic bag and identified for analysis as sham or active by means of a numerical code known only to the data coordinating center. Study devices were assigned randomly in a 1:1 ratio on the basis of permuted blocks of concealed size within strata defined by the participating geographic site and further defined within the site by the participating EMS agency or subagency. EMS personnel were instructed to use the devices in the assigned, sequential order. Patients, investigators, study co-

ordinators, and all persons caring for the patient were unaware of the treatment assignments. Patients were considered to be enrolled in the study once an ITD package was opened.

INTERVENTION

The first EMS responders to arrive at the scene of the arrest who were equipped with a randomly assigned ITD (active or sham) attached the device between the ventilation bag and face mask or between the bag and an advanced airway (e.g., Combitube [Tyco Healthcare Group], laryngeal mask airway, or endotracheal tube) (Fig. 1 in the Supplementary Appendix). Responders were encouraged to implement use of the device within 5 minutes after their arrival or as soon as clinically possible. Standard CPR in most agencies was provided with a 30:2 ratio of chest compressions to ventilations. Several agencies used continuous compressions with interposed ventilations at a ratio of 10:1.

To avoid impeding inspiration in patients whose spontaneous breathing was unrecognized, EMS providers were instructed to remove the ITD immediately on the return of spontaneous circulation but to reapply it for recurrent cardiac arrest. If the device filled with fluid, it was removed and cleared, the patient's airway was suctioned, and the device was reapplied. If the device again filled with fluid, its use was permanently discontinued. Use of the ITD was terminated on arrival at the hospital.

STUDY OUTCOMES

The primary outcome was survival to hospital discharge with satisfactory functional status, defined as a score of 3 or less on the modified Rankin scale, a validated scale ranging from 0 to 6 that is commonly used for measuring the performance of daily activities by people who have had a stroke. Lower scores indicate better performance; scores of 4 or higher indicate severe disability or death. Data used to determine the score on the Rankin scale were abstracted from the clinical record.[12]

Secondary outcomes included return of spontaneous circulation on arrival at the emergency department, survival to hospital admission, and survival to hospital discharge. Adverse events were recorded by the responders and other clinicians involved in the care of the patients on the basis of EMS records, hospital charts, and autopsy reports and were monitored by an independent data and safety monitoring board.

TRAINING OF EMS PERSONNEL

EMS personnel were trained in ITD function, proper use of the ITD, and all aspects of protocol implementation, with an emphasis on the optimal performance of CPR according to local guidelines.[13] The trial included a run-in phase; EMS personnel were required to provide evidence of acceptable performance to an internal monitoring committee before they were permitted to participate in the main trial. Retraining occurred at periodic intervals throughout the trial, and the committee monitored CPR performance and compliance with the protocol.

STATISTICAL ANALYSIS

We estimated that a sample of 14,154 patients in the analysis population (7077 per study group) would be needed to achieve 90% power to detect a 25% relative improvement in the primary outcome with the use of the active ITD as compared with the sham ITD (6.7% vs. 5.3%).[11] The data and safety monitoring board monitored trial progress and safety and used formal stopping boundaries.

Adverse events classified as possibly related to ITD use (ITD not removed by rescuer after the return of spontaneous circulation, suspected device failure, pulmonary edema, and airway bleeding) were monitored in all patients who had an active or sham ITD applied either during the run-in phase or in the main trial (defined as the safety population). The intention-to-treat population included all patients for whom an ITD package was opened during the main trial. The primary effectiveness analysis was performed in a modified intention-to-treat population, which included all patients who had an ITD (active or sham) applied during the main trial but excluded those who had cardiac arrest due to hanging, drowning, electrocution, or strangulation or for whom the response time exceeded 15 minutes.[11]

For the primary analysis, we used a z statistic to compare the rates of survival to hospital discharge with satisfactory functional status in the two groups. To adjust for group sequential monitoring, the point estimate was bias-adjusted,[14] and confidence intervals and P values were calculated from the maximum likelihood–based ordering of the outcome.[15] Between-group differences in the rates of survival to discharge with satisfactory functional status, adjusted for baseline characteristics, were estimated with the use of a multiple

Table 1. Characteristics before Randomization in the Modified Intention-to-Treat Population.*

Characteristic	Sham ITD (N=4345)	Active ITD (N=4373)	Not Enrolled (N=3613)
Age — yr†	66.6±16.5	67.2±16.4	66.0±17.2
Male sex — no. of patients/total no. (%)	2790/4345 (64.2)	2838/4372 (64.9)	2086/3281 (63.6)
Obvious cause of arrest — no. of patients/total no. (%)‡	128/4345 (2.9)	91/4373 (2.1)	197/3279 (6.0)
Public location — no. of patients/total no. (%)	621/4345 (14.3)	609/4373 (13.9)	544/3281 (16.6)
Witness status — no. of patients/total no. (%)			
EMS witnessed	331/4345 (7.6)	367/4373 (8.4)	624/3281 (19.0)
Bystander witnessed	1794/4345 (41.3)	1754/4373 (40.1)	1118/3281 (34.1)
Bystander performed CPR — no. of patients/total no. (%)			
Yes	1681/4345 (38.7)	1672/4373 (38.2)	1039/3281 (31.7)
No	2440/4345 (56.2)	2474/4373 (56.6)	2133/3281 (65.0)
Time from dispatch to first EMS arrival — min	5.8±2.2	5.8±2.3	6.6±4.6§
Time from dispatch to first EMS arrival ≤4 min — no. of patients/total no. (%)	913/4345 (21.0)	887/4373 (20.3)	541/3573 (15.1)
Time from dispatch to first arrival of ALS providers — min¶	9.0±4.9	9.0±4.9	10.3±7.3
Treated by ALS providers — no. of patients/total no. (%)	4261/4345 (98.1)	4293/4373 (98.2)	3343/3613 (92.5)
Site — no. of patients (%)			
A	168 (3.9)	189 (4.3)	120 (3.3)
B	373 (8.6)	373 (8.5)	611 (16.9)
C	387 (8.9)	371 (8.5)	102 (2.8)
D	1355 (31.2)	1362 (31.1)	1530 (42.3)
E	165 (3.8)	153 (3.5)	125 (3.5)
F	132 (3.0)	139 (3.2)	81 (2.2)
G	978 (22.5)	977 (22.3)	319 (8.8)
H	667 (15.4)	686 (15.7)	598 (16.6)
I	29 (0.7)	30 (0.7)	72 (2.0)
J	91 (2.1)	93 (2.1)	55 (1.5)

* Plus–minus values are means ±SD. The P values for all comparisons were not significant (≥0.05) unless otherwise stated. ALS denotes advanced life support, EMS emergency medical services, and ITD impedance threshold device.
† The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 4337, 4365, and 3264, respectively.
‡ Obvious causes of arrest included but were not limited to drug poisoning, foreign-body obstruction, terminal illness, and respiratory compromise. The difference between sham-ITD and active-ITD groups was significant (P<0.05).
§ The total number of patients in the not-enrolled group was 3573.
¶ The comparison with respect to the time from dispatch to first arrival of advanced life support was based only on the cases for which advanced life support was on the scene and the elapsed time was known (4259, 4291, and 3338 in the sham-ITD, active-ITD, and not-enrolled groups, respectively).

linear regression model with bootstrap standard errors to allow for the binary nature of the outcome. Mean scores on the modified Rankin scale were compared between study groups with the use of a two-sample t-test with unequal variances. All reported P values are based on two-sided tests; a P value of less than 0.05 was considered to indicate statistical significance. Heterogeneity of the treatment effect across sites was assessed by means of the weighted least-squares chi-square statistic with 9 degrees of freedom.[16]

RESULTS

STUDY PARTICIPANTS

The first EMS system entered the run-in phase in June 2007. All 10 sites halted enrollment in November 2009, when the data and safety monitoring board recommended termination because interim analysis showed that the findings were not likely to change with continuation of the study. Of the 13,924 patients with cardiac arrest who were screened, 12,863 potentially eligible

patients were identified; 9220 patients (71.7% of those eligible) were randomly assigned to either the sham ITD (4601) or the active ITD (4619). On the basis of a priori exclusion criteria,[11] the primary outcome was subsequently assessed for 4345 participants in the sham-ITD group and 4373 participants in the active-ITD group (Fig. 2 in the Supplementary Appendix). Differences in prerandomization and postrandomization characteristics of the patients, as well as characteristics of EMS and hospital treatments, were not considered to be clinically significant. Prerandomization and postrandomization characteristics of the 3613 patients who were eligible but not enrolled in the trial are also reported and differed with respect to several of the characteristics (Tables 1 and 2).

OUTCOMES

A total of 260 of the 4345 patients (6.0%) in the sham-ITD group and 254 of the 4373 patients (5.8%) in the active-ITD group survived to hospital discharge with a modified Rankin scale score of 3 or less (risk difference adjusted for sequential monitoring, −0.1 percentage points; 95% confi-

Table 2. Patient Characteristics and Treatments Received after Randomization in the Modified Intention-to-Treat Population.*

Characteristic	Sham ITD (N=4345)	Active ITD (N=4373)	Not Enrolled (N=3613)
Time from arrival of ITD-equipped EMS personnel to ITD application			
Median (interquartile range) — min	4.0 (2.4–6.4)	4.0 (2.4–6.5)	
Interquartile range			
≤5 min — no. of patients (%)	2589/4114 (62.9)	2539/4127 (61.5)	
First rhythm interpretation — no. of patients (%)			
Shockable VT or VF	1096 (25.2)	1040 (23.8)	763 (21.1)
Pulseless electrical activity	1007 (23.2)	1080 (24.7)	703 (19.5)
Asystole	1946 (44.8)	1903 (43.5)	1228 (34.0)
AED used, no shock advised, and no recording available	273 (6.3)	327 (7.5)	473 (13.1)
Perfusing rhythm after initial CPR	6 (0.1)	5 (0.1)	7 (0.2)
Unknown or could not be determined	17 (0.4)	18 (0.4)	439 (12.2)
Shocks applied			
No. of patients/total no. (%)	1791/4344 (41.2)	1733/4368 (39.7)	1159/3270 (35.4)
No. of shocks, if given†	3.3±2.8	3.3±2.8	2.7±2.5
Prehospital intubation — no. of patients (%)			
Attempted	3620 (83.3)	3644 (83.3)	2047/3281 (62.4)
Successful	3312 (76.2)	3332 (76.2)	1738/3281 (53.0)
CPR process measures up to 5 min or until intubation			
Pause before shock — sec‡	16.7±11.7	17.3±12.1	16.8±11.5
Pause after shock — sec§	8.1±8.0	8.0±7.6	11.2±25.5
Compression rate — no./min¶	107.4±19.2	107.3±18.1	109.3±21.7
Compression depth — mm‖	42.4±12.0	42.8±12.2	41.3±11.9
CPR fraction**	0.69±0.2	0.69±0.2	0.67 (0.2)
Drugs administered before arrival at hospital — no. of patients/total no. (%)			
Epinephrine††	3791/4336 (87.4)	3856/4361 (88.4)	2044/3244 (63.0)
Sodium bicarbonate	1033/4336 (23.8)	1066/4360 (24.4)	339/3244 (10.5)
Atropine	3009/4336 (69.4)	3077/4360 (70.6)	1721/3244 (53.1)
Lidocaine	597/4336 (13.8)	595/4360 (13.6)	183/3244 (5.6)
Amiodarone‡‡	428/4336 (9.9)	377/4360 (8.6)	249/3244 (7.7)

Table 2. (Continued.)

Characteristic	Sham ITD (N=4345)	Active ITD (N=4373)	Not Enrolled (N=3613)
Coenrollment in companion study — no. of patients (%)			
Later-analysis group	1860 (42.8)	1815 (41.5)	1368 (37.9)
Early-analysis group	1634 (37.6)	1632 (37.3)	1128 (31.2)
Not enrolled in companion study	851 (19.6)	926 (21.2)	1117 (30.9)
Hospital procedures — no. of patients/total no. (%)§§			
Hypothermia	554/1147 (48.3)	543/1142 (47.5)	292/906 (32.2)
Coronary catheterization	358/1147 (31.2)	324/1142 (28.4)	312/906 (34.4)
Implantable cardioverter–defibrillator	110/1147 (9.6)	105/1142 (9.2)	71/906 (7.8)

* Plus–minus values are means ±SD. The P values for all comparisons were not significant (≥0.05) unless otherwise noted. AED denotes automated external defibrillator, ITD impedance threshold device, VF ventricular fibrillation, and VT ventricular tachycardia.
† The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 1788, 1731, and 1156, respectively.
‡ The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 1227, 1220, and 503, respectively.
§ The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 1250, 1235, and 539, respectively.
¶ The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 2786, 2739, and 1370, respectively.
‖ The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 1888, 1862, and 924, respectively.
** The CPR fraction is the percentage of time that compressions were given during resuscitation. The total numbers of patients in the sham-ITD, active-ITD, and not-enrolled groups were 2791, 2743, and 1372, respectively.
†† The mean doses of epinephrine were 3.7±1.9 (in 3789 patients), 3.7±2.0 (in 3851), and 3.3±2.0 (in 2036) for the sham-ITD, active-ITD, and not-enrolled groups, respectively.
‡‡ The difference between the sham-ITD group and the active-ITD group was significant (P<0.05).
§§ A total of 1149 patients in the sham-ITD group, 1143 in the active-ITD group, and 909 in the not-enrolled group were admitted to the hospital. Data regarding procedures were available for 1147, 1142, and 906 patients, respectively.

dence interval, –1.1 to 0.8; P=0.71) (Table 3). There were also no significant between-group differences in the primary outcome with the analysis adjusted for baseline characteristics, in any of the secondary outcomes, or in adverse events as assessed in the safety population.

SUBGROUP ANALYSES

There were no significant differences in a priori subgroup analyses between the sham-ITD and active-ITD groups (Fig. 3 in the Supplementary Appendix). Post hoc, exploratory subgroup analyses showed that for subgroups defined by the CPR fraction (the percentage of time that compressions were delivered during resuscitation), patients in the second-lowest quartile (59.9 to 71.0%) who were treated with an active ITD had significant improvement in survival to hospital discharge with satisfactory functional status (P<0.01; P=0.006 for interaction). There were no significant differences between use of the sham ITD and use of the active ITD in any other exploratory subgroup analysis (Fig. 3 in the Supplementary Appendix).

Variation in treatment effect from site to site was consistent with random variation. The chi-square test for heterogeneity was not significant (P=0.4).

DISCUSSION

Physiological studies in animals and humans have suggested that interventions capable of decreasing mean intrathoracic pressure can augment the return of venous blood to the heart and improve hemodynamics during CPR.[3-5,7] Despite such findings, this large effectiveness trial did not confirm a survival advantage with the use of an active ITD during standard CPR in patients with nontraumatic, out-of-hospital cardiac arrest.

One possible explanation for the neutral results is that, despite the evidence cited, the ITD may not generate the physiological effects that have been proposed. Two studies in animals that were published after the present trial began enrollment showed no improvement in hemodynamics or survival with application of the ITD during standard CPR.[17,18]

A second possible explanation is that use of the active ITD by the participating EMS systems did not recreate the physiological effects seen in some of the experimental studies.[3-5,7] Delayed application of the ITD, failure to prevent airway leaks, and suboptimal performance of CPR can interfere with the hemodynamic improvements that are associated with ITD use.[19-22] For these reasons, the ROC

Table 3. Outcomes in the Modified Intention-to-Treat (ITT) and Safety Populations.*

Outcome	Sham ITD (N=4345)	Active ITD (N=4373)	Percentage-Point Difference (95% CI)	P Value
Modified ITT population				
Transported to hospital — no. of patients (%)	2451 (56.4)	2448 (56.0)	−0.4 (−2.5 to 1.7)	0.69
ROSC on arrival at emergency department — no. of patients (%)	1206 (27.8)	1186 (27.1)	−0.6 (−2.5 to 1.2)	0.51
Survival to hospital admission — no. of patients (%)	1139/4335 (26.3)	1140/4370 (26.1)	−0.2 (−2.0 to 1.7)	0.84
Survival to discharge — no. of patients (%)	355 (8.2)	357 (8.2)	0.0 (−1.2 to 1.1)	0.99
Score on modified Rankin scale — no. of patients (%)†				
≤3‡	260 (6.0)	254 (5.8)	−0.1 (−1.1 to 0.8)	0.71
0	73 (1.7)	81 (1.9)		
1	87 (2.0)	77 (1.8)		
2	28 (0.6)	22 (0.5)		
3	72 (1.7)	74 (1.7)		
4	57 (1.3)	55 (1.3)		
5	38 (0.9)	48 (1.1)		
6	3990 (91.8)	4016 (91.8)		
Mean modified Rankin score	5.69±1.15	5.69±1.14	0.01 (−0.04 to 0.05)	0.83
Safety population§				
ITD not removed after ROSC — no. of patients/total no. (%)	140/5790 (2.4)	144/5802 (2.5)	0.1 (−0.5 to 0.6)	0.61
Suspected device failure — no. of patients/total no. (%)	4/5790 (0.1)	9/5802 (0.2)	0.1 (0.0 to 0.2)	0.17
Pulmonary edema — no. of patients/total no. (%)	346/5790 (6.0)	336/5802 (5.8)	−0.2 (−1.0 to 0.7)	0.67
Airway bleeding — no. of patients/total no. (%)	176/5790 (3.0)	179/5802 (3.1)	0.0 (−0.6 to 0.7)	0.89

* Plus–minus values are means ±SD. ITD denotes impedance threshold device, and ROSC return of spontaneous circulation.
† The modified Rankin scale ranges from 0 to 6, with higher numbers indicating greater disability.
‡ The risk differences, confidence intervals, and P values were adjusted for sequential monitoring.
§ The total numbers for the sham-ITD and active-ITD groups are higher (5790 and 5802, respectively) because they include the safety population in both the run-in phase (1107 patients in the sham-ITD group and 1115 patients in the active-ITD group) and the main trial (4683 patients in the sham-ITD group and 4687 patients in the active-ITD group).

investigators implemented comprehensive training, retraining, electronic monitoring of the CPR process, and follow-up quality-assurance monitoring. The quality of the CPR provided was associated with outcomes in the sham-ITD group that were better than expected. Therefore, it is not likely that EMS systems would apply the ITD in a more operationally efficacious way than they were applied in this study.

Another possible explanation is that application of the active ITD produced the physiological effects seen in experimental studies but did not improve clinical outcomes. It is possible that failure to remove the ITD immediately after successful resuscitation, with the resulting increased work of breathing, increases interstitial lung fluid and left-sided pressures and worsens heart failure, or that such failure increases venous pressure, decreasing cerebral perfusion pressure in the resuscitated state. Other interventions (e.g., the administration of epinephrine) might exacerbate these potential complications.

Several limitations of the trial should be noted. The investigators did not directly measure hemodynamics, intrathoracic pressure, ventilation rate and duration, or the effects of ITD use during gasping and spontaneous ventilation. CPR process measures were not recorded in all cases. Although use of the modified Rankin scale has been validated for assessing the effects of stroke, it lacks validation for cardiac arrest. In only 61.5% of patients who received the active ITD was it placed

within 5 minutes after the arrival of EMS personnel.

Another factor of potential importance that was not measured in this study is chest recoil.[22] Loss of elastic recoil of the chest can occur over time during standard CPR.[23] Since the purpose of the ITD is to enhance negative intrathoracic pressure by preventing passive air inflow during chest recoil, loss of such recoil is a potential limitation in achieving the desired physiological result. A recent study showed that combining the use of an ITD and active compression–decompression CPR significantly increases survival to hospital discharge with satisfactory function, as compared with standard CPR.[24]

In conclusion, we compared use of an active ITD with use of a sham ITD during standard CPR in patients with nontraumatic, out-of-hospital cardiac arrest. Use of the active ITD did not significantly improve survival with satisfactory function.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. Eisenberg MS, Psaty BM. Cardiopulmonary resuscitation: celebration and challenges. JAMA 2010;304:87-8.
2. Andreka P, Frenneaux MP. Haemodynamics of cardiac arrest and resuscitation. Curr Opin Crit Care 2006;12:198-203.
3. Lurie KG, Zielinski T, McKnite S, Aufderheide TP, Voelckel W. Use of an inspiratory impedance valve improves neurologically intact survival in a porcine model of ventricular fibrillation. Circulation 2002;105:124-9.
4. Aufderheide TP, Lurie KG. Vital organ blood flow with the impedance threshold device. Crit Care Med 2006;34:Suppl:S466-S473.
5. Yannopoulos D, Sigurdsson G, McKnite S, Benditt D, Lurie KG. Reducing ventilation frequency combined with an inspiratory impedance device improves CPR efficiency in swine model of cardiac arrest. Resuscitation 2004;61:75-82.
6. Aufderheide TP, Pirrallo RG, Provo TA, Lurie KG. Clinical evaluation of an inspiratory impedance threshold device during standard cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest. Crit Care Med 2005;33:734-40.
7. Pirrallo RG, Aufderheide TP, Provo TA, Lurie KG. Effect of an inspiratory impedance threshold device on hemodynamics during conventional manual cardiopulmonary resuscitation. Resuscitation 2005;66:13-20.
8. Thayne RC, Thomas DC, Neville JD, van Dellen A. Use of an impedance threshold device improves short-term outcomes following out-of-hospital cardiac arrest. Resuscitation 2005;67:103-8.
9. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care part 6: CPR techniques and devices. Circulation 2005;112:Suppl:IV47-IV50.
10. Stiell IG, Nichol G, Leroux BG, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. N Engl J Med 2011;365:787-97.
11. Aufderheide TP, Kudenchuk PJ, Hedges JR, et al. Resuscitation Outcomes Consortium (ROC) PRIMED cardiac arrest trial methods part 1: rationale and methodology for the impedance threshold device (ITD) protocol. Resuscitation 2008;78:179-85.
12. Lai SM, Duncan PW. Stroke recovery profile and the Modified Rankin assessment. Neuroepidemiology 2001;20:26-30.
13. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112:Suppl:IV-1–IV-203.
14. Whitehead J. Sample sizes for phase II and phase III clinical trials: an integrated approach. Stat Med 1986;5:459-64.
15. Emerson SS, Fleming TR. Interim analyses in clinical trials. Oncology (Williston Park) 1990;4:126-33.
16. DerSimonian R, Laird N. Meta-analy-

sis in clinical trials. Control Clin Trials 1986;7:177-88.
17. Menegazzi JJ, Salcido DD, Menegazzi MT, et al. Effects of an impedance threshold device on hemodynamics and restoration of spontaneous circulation in prolonged porcine ventricular fibrillation. Prehosp Emerg Care 2007;11:179-85.
18. Mader TJ, Kellogg AR, Smith J, et al. A blinded, randomized controlled evaluation of an impedance threshold device during cardiopulmonary resuscitation in swine. Resuscitation 2008;77:387-94.
19. Aufderheide TP, Alexander C, Lick C, et al. From laboratory science to six emergency medical services systems: new understanding of the physiology of cardiopulmonary resuscitation increases survival rates after cardiac arrest. Crit Care Med 2008;36:Suppl:S397-S404.
20. Aufderheide TP, Sigurdsson G, Pirrallo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. Circulation 2004;109:1960-5.
21. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA 2005;293:299-304.
22. Yannopoulos D, McKnite S, Aufderheide TP, et al. Effects of incomplete chest wall decompression during cardiopulmonary resuscitation on coronary and cerebral perfusion pressures in a porcine model of cardiac arrest. Resuscitation 2005;64:363-72.
23. Tomlinson AE, Nysaether J, Kramer-Johansen J, Steen PA, Dorph E. Compression force-depth relationship during out-of-hospital cardiopulmonary resuscitation. Resuscitation 2007;72:364-70.
24. Aufderheide TP, Frascone RJ, Wayne MA, et al. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. Lancet 2011;377:301-11.