Impedance Threshold Device Combined With High-Quality Cardiopulmonary Resuscitation Improves Survival With Favorable Neurological Function After Witnessed Out-of-Hospital Cardiac Arrest

Atsushi Sugiyama, MD, PhD; Sue Duval, PhD; Yuji Nakamura, PhD; Katsunori Yoshihara, MD, PhD; Demetris Yannopoulos, MD, PhD

Background: The quality of cardiopulmonary resuscitation (CPR) has been recently shown to affect clinical outcome. The Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis (PRIMED) trial showed no differences in outcomes with an active vs. sham impedance threshold device (ITD), a CPR adjunct that enhances circulation. It was hypothesized the active ITD would improve survival with favorable neurological outcomes in witnessed out-of-hospital cardiac arrest patients when used with high-quality CPR.

Methods and Results: Using the publicly accessible ROC PRIMED database, a post-hoc analysis was performed on all witnessed subjects with both compression rate and depth data (n=1,808) who received CPR within the study protocol definition of adequate CPR quality (compression rate 80–120/min and depth 4–6 cm; n=929). Demographics were similar between sham and active ITD groups. In witnessed subjects who received quality CPR, survival with favorable neurological function was 11.9% for the active ITD subjects (56/470) vs. 7.4% for the sham (34/459) (odds ratio 1.69 [95% confidence interval 1.08, 2.64]). There were no statistically significant differences for this primary outcome when CPR was performed outside the boundaries of the definition of adequate CPR quality. Multivariable models did not change these associations.

Conclusions: An active ITD combined with adequate-quality conventional CPR has the potential to significantly improve survival after witnessed cardiac arrest. (Circ J 2016; 80: 2124–2132)

Key Words: Cardiopulmonary resuscitation; Impedance threshold device; Mechanophysiology; ROC PRIMED trial; Witnessed cardiac arrest

Cardiac arrest remains a leading cause of unexpected sudden death in Japan. Recent efforts to improve survival after out-of-hospital cardiac arrest (OHCA) have been complicated by issues related to the quality of cardiopulmonary resuscitation (CPR) delivered by first responders. There is increasing evidence to suggest that the manner in which chest compressions and ventilations are delivered has a significant effect on the outcome of CPR. In addition, challenges related to the quality of CPR make it more difficult to assess new medical technologies, especially those designed to improve the outcome after OHCA. For example, defibrillation therapy is more effective when provided quickly or after effective bystander CPR. There is strong support for the need for high-quality CPR even before delivering the first shock.

One device that has shown significant potential to improve survival after cardiac arrest is called the impedance threshold device (ITD). As described in Supplementary Methods, this device can be attached to a facemask or advanced airway, and functions by impeding respiratory gases from entering the lungs during the decompression phase of CPR, thereby augmenting the intrathoracic vacuum that develops each time the chest wall recoils. The ITD also reduces the total volume of respiratory gas in the lungs between each positive pressure breath during CPR. These mechanisms of action enhance the refilling of the heart after each compression, lower the intracranial pressure, and improve blood flow to the heart and brain during CPR.

The ITD has been evaluated in bench testing, animals, and...
Given the recent recognition that CPR quality can significantly affect outcomes,\textsuperscript{8} the data from the ROC PRIMED study was re-analyzed in the present study using the database that became recently available to the public through the US Freedom of Information Act. The focus was on patients with the highest likelihood of survival: those with a witnessed arrest when efforts to resuscitate, including a call for help, were started immediately. The hypothesis was that subjects with a witnessed OHCA receiving high-quality CPR with the active ITD have a greater likelihood of survival to hospital discharge with favorable neurologic function compared with a sham device.

The database was also used to calculate the rate and depth of CPR with both the sham and active ITD necessary to optimize survival to hospital discharge with favorable brain function.

**Methods**

The current study was conducted independently of the United States National Institutes of Health (NIH) and in collaboration with investigators from the Minnesota Resuscitation Consortium at the University of Minnesota. The NIH database was accessed through the Freedom of Information Act. The Human Subjects Committees at the University of Minnesota and Toho...
periods of time from arrest to start of CPR have a poor prognosis. Additional secondary endpoints using the same witnessed arrest population were performed to determine the “sweet spot” for CPR and whether or not there would have been a positive effect from active ITD use if rescuers were to have followed the new 2015 AHA Guidelines. The compression rate and depth needed to optimize survival with favorable brain function were also calculated from the same data set.

### Statistical Analysis

Continuous variables are reported as the mean±SD and categorical variables by frequency and percentage. Comparisons between sham and active ITD were performed with t-tests or chi-square tests as appropriate. Logistic regression was used to assess the relationship between CPR quality and survival to hospital discharge with favorable neurological function. Multivariable logistic regression models were adjusted for age, sex and initial rhythm (except in the subgroup of patients with shockable rhythms), and further models also adjusted for bystander CPR and time from dispatch to first EMS arrival.

A response surface modeling approach was used to estimate the values of rate and depth that optimized the proportion of survivors in the 130 cells defined by rate (10 levels) and depth (13 levels). Rate was defined as the midpoint of the interval (ie, 95 was used to represent the interval 90–100 compressions per min, and depth was rounded to the nearest 0.5 cm). Both compression rate and depth data were measured in 3,749 subjects during the pivotal study, but these data were not available to rescuers to guide CPR quality. The rate and depth data were retrieved after the study was completed. In the current analysis, these rate and depth quality assessment measurements were used to determine survival with favorable brain function when using an active ITD with conventional manual CPR performed according to the recommendations of the 2005 AHA Guidelines.

Data were collected as recommended by the Utstein Guidelines and analyzed to determine the primary and secondary endpoints. The primary endpoint of the current post-hoc analysis, as in the ROC PRIMED study itself, was survival to hospital discharge associated with favorable neurological function as determined by the modified Rankin scoring system. The primary analysis focused on subjects with a witnessed arrest for whom compression rate and depth data were available. The witnessed arrest population was selected a priori because it is well established that patients with unknown

### University determined that no further review for this study was needed.

### Study Protocol

The ROC PRIMED study subjects were those with an out-of-hospital non-traumatic cardiac arrest of presumed cardiac etiology. The methodology and primary study results have been previously described. Quality CPR, defined as an average chest compression rate between 80 and 120 per min with an average depth of 4–6 cm, was prespecified and used to determine whether the study sites qualified for transition from the run-in phase to the pivotal study phase; sites were allowed to enroll patients in the pivotal phase of the study only if they demonstrated a high level of CPR quality. Consistent with the American Heart Association (AHA) recommendations at the time the study was started in 2005, the ROC PRIMED recommended compression rate was 100 per min and depth was 5 cm. Both compression rate and depth data were measured in 3,749 subjects during the pivotal study, but these data were not available to rescuers to guide CPR quality. The rate and depth data were retrieved after the study was completed. In the current analysis, these rate and depth quality assessment measurements were used to determine survival with favorable brain function when using an active ITD with conventional manual CPR performed according to the recommendations of the 2005 AHA Guidelines.

### Table 1. (A) Characteristics of 4,247 Subjects With a Witnessed Arrest (EMS or Bystander), (B) Characteristics of 1,808 Subjects With a Witnessed Arrest, and for Whom Compression Rate and Depth Were Recorded

|                  | Sham ITD (n=2,125) | Active ITD (n=2,122) | Sham ITD (n=928) | Active ITD (n=880) |
|------------------|---------------------|----------------------|------------------|--------------------|
| **A**            |                     |                      |                  |                    |
| **B**            |                     |                      |                  |                    |
| Age (years)      | 67.0±15.3           | 67.7±15.7            | 67.6±15.0        | 67.7±15.7          |
| Male             | 1,424 (67%)         | 1,438 (68%)          | 606 (65%)        | 614 (70%)          |
| Public location  | 446 (21.0%)         | 402 (19.9%)          | 186 (20.0%)      | 161 (18.3%)        |
| Bystander CPR    | 867 (40.8%)         | 847 (39.9%)          | 368 (39.7%)      | 332 (37.7%)        |
| Time from dispatch to first EMS arrival (min) | 5.9±2.3 | 5.9±2.3 | 5.9±2.2 | 5.8±2.1 |
| Time from dispatch to first EMS arrival ≤4 min | 419 (19.7%) | 423 (19.9%) | 174 (18.8%) | 148 (16.8%) |
| Time from dispatch to first arrival of ALS providers (min) | 9.2±5.2 | 9.2±5.3 | 8.8±4.5 | 8.7±4.8 |
| Treated by ALS providers | 2,080 (97.9%) | 2,079 (98.0%) | 922 (99.4%) | 878 (99.8%) |
| First rhythm interpretation | | | | |
| Shockable VT or VF | 770 (36.2%) | 703 (33.1%) | 330 (35.6%) | 292 (33.2%) |
| Pulseless electrical activity | 642 (30.2%) | 702 (33.1%) | 275 (29.6%) | 299 (34.0%) |
| Asystole | 588 (27.7%) | 558 (26.3%) | 298 (32.1%) | 265 (30.1%) |
| AED used, no shock advised, and no recording available | 115 (5.4%) | 146 (6.9%) | 25 (2.7%) | 24 (2.7%) |
| Perfusing rhythm after initial CPR | 5 (0.24%) | 4 (0.19%) | 0 | 0 |
| Unknown or could not be determined | 5 (0.24%) | 9 (0.42%) | 0 | 0 |
| Adrenaline dose (mg) | 3.7±2.0* | 3.7±2.2* | 3.6±1.8** | 3.6±1.9** |

*In 1,836 sham ITD and 1,852 active ITD patients who received adrenaline. **In 820 sham ITD and 801 active ITD patients who received adrenaline. AED, automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ITD, impedance threshold device; VF, ventricular fibrillation; VT, ventricular tachycardia.
Results

The original ROC PRIMED study described the results from 8,718 subjects and the principal findings reported in the primary analysis were able to be replicated in the present study using the publicly available database. Of these, 4,247 subjects had a witnessed arrest. The current analysis focused on subjects for whom CPR quality measures were available related to chest compression rate and depth and who had a witnessed arrest. Figure 1 is a flow chart of all witnessed arrest patients who survived to hospital discharge with favorable neurologic function.

As shown in Table 1A, the demographics of all 4,247 subjects with a witnessed arrest treated with a sham vs. active device were similar regarding age, sex, use of bystander CPR, dose of adrenaline, average time from call for help to first chest compressions, and the frequency of the first recorded rhythm. The relative frequency of ventricular fibrillation (VF) was slightly higher in the sham group (36.2%) vs. the active group (33.1%) for the first recorded rhythm (P=0.03).

Table 1B presents the characteristics and demographics of all 1,808 subjects with a witnessed arrest for whom both CPR rate and depth data were recorded and monitored during the study. There were no significant differences in the characteristics or demographics of this subject group when comparing treatment with a sham vs. active ITD. The primary study analysis population in this report was restricted to subjects with a witnessed arrest for whom both compression rate and depth data were available.

The characteristics of all 929 subjects with a witnessed arrest treated with high-quality CPR, defined as receiving CPR with an average chest compression rate between 80 and 120 per min and an average depth of 4–6 cm, are shown in Table 2. There were no significant differences in characteristics or demographics when comparing treatment with a sham vs. active ITD.

Quality of CPR received affected the outcomes of subjects with a witnessed arrest when the compression rate and depth were known. As shown in Table 3, when compression rate and depth were within the range recommended by the AHA and International Liaison Committee on Resuscitation (ILCOR) Guidelines, survival to hospital discharge with favorable neurologic function was significantly better. Subjects with a witnessed OHCA treated with high-quality CPR and an active ITD had a significantly greater likelihood of survival to hospital discharge with favorable neurologic function (11.9%) than those with high-quality CPR and a sham ITD (7.4%) (odds ratio [OR] 1.69; 95% confidence interval [CI] 1.08, 2.64). Multivariable logistic regression analyses demonstrated that the observed enhanced survival with favorable neurologic function was maintained after adjusting for the initial rhythm, age, and sex (Table 3, Model 1). The respective OR and CI for this adjusted primary study endpoint analysis was 1.79 [1.10, 2.91]. Further adjustment by bystander CPR and time from dispatch to first EMS arrival slightly augmented the association (Table 3, Model 2). By contrast, in the absence of high-quality CPR (defined as a compression rate <80 or >120 per min and compression depth <4 cm or >6 cm) there was no difference in the primary study outcome between the active and sham ITD (P=0.19 unadjusted, P=0.15 and P=0.26 for the adjusted models, respectively) (Table 3).

Although the primary a priori endpoint of this re-analysis was to focus on all patients with a witnessed OHCA, the subgroup of patients with a witnessed arrest and a first recorded rhythm of VF or ventricular tachycardia (VT) was also assessed. As shown in Table 3, there was an absolute 9.4% increase in survival with favorable brain function in the VF/VT subjects treated with high-quality CPR and active ITD (28.3%) vs. sham (18.9%) (P=0.043 unadjusted, 0.049 and 0.033 in the adjusted models, respectively) (Table 3).

In the ROC PRIMED study protocol, a chest compression rate between 80 and 120 per min was defined as adequate. In the current study an additional analysis was performed (Table 4), narrowing the compression rate range further to 90–110, to determine whether tightening of the quality metrics would further improve outcomes for subjects treated with an active ITD; survival was even better with the more narrow range.

To further examine the effect of high-quality CPR on outcome,

---

**Table 2. Demographics and Characteristics of Subjects With a Witnessed Arrest Who Received High-Quality CPR, Defined as an Average Chest Compression Rate Between 80 and 120 per min With an Average Depth of 4–6 cm**

| Characteristic | Sham ITD (n=459) | Active ITD (n=470) | P value |
|---------------|-----------------|-------------------|---------|
| Age (years)   | 67.1±14.3       | 67.5±15.0         | 0.62    |
| Sex           |                 |                   |         |
| Male          | 298 (65%)       | 326 (69%)         | 0.15    |
| Female        | 161 (35%)       | 144 (31%)         |         |
| Public location |               |                   |         |
| Rural         | 146 (32%)       | 147 (31%)         | 0.91    |
| Urban         | 313 (68%)       | 323 (69%)         |         |
| Bystander performed CPR | 98 (21.4%) | 91 (19.4%) | 0.45 |
| Time from dispatch to first EMS arrival (min) | 5.9±2.1 | 5.7±2.0 | 0.12 |
| Time from dispatch to first EMS arrival ≤4 min | 77 (16.8%) | 85 (18.1%) | 0.6 |
| Time from dispatch to first arrival of ALS providers (min) | 8.9±4.0 | 8.8±4.6 | 0.65 |
| Treated by ALS providers | 458 (99.8%) | 468 (99.6%) | 1.0 |
| First rhythm interpretation | | | |
| Shockable VT or VF | 169 (36.8%) | 177 (37.7%) |         |
| Pulseless electrical activity | 138 (30.1%) | 140 (29.8%) |         |
| Asystole | 142 (30.9%) | 139 (29.6%) |         |
| AED used, no shock advised, and no recording available | 10 (2.2%) | 14 (3.0%) |         |
| Perfusing rhythm after initial CPR | 0 | 0 | |
| Unknown or could not be determined | 0 | 0 | |
| Adrenaline dose (mg)* | 3.7±1.8 | 3.6±2.0 | 0.83 |

*In 408 sham ITD and 428 active ITD patients who received adrenaline. Abbreviations as in Table 1.
To further explore the importance of CPR quality on outcome, the outcomes of all witnessed arrests were examined independent of CPR quality as a secondary endpoint. There were no significant differences in witnessed OHCA outcomes between the active ITD (9.7%) vs. sham (9.5%) when the quality of CPR was not taken into consideration (P=0.78). In addition, hospital discharge rates with favorable neurological function in witnessed arrests using a compression rate of 100–120 per min and a depth of 4–6 cm, the recommended rate and depth based on consensus of experts in the 2015 AHA Guidelines, were examined. Based on these guidelines, subjects with a witnessed arrest treated with a sham device would have an overall survival with good neurological outcome of 9.0% (23/256) vs. 12.4% (34/275) for the active ITD group (P=0.20).

**Table 3. Effect of CPR Quality on Survival to Hospital Discharge With Favorable Neurological Function in Subjects With a Witnessed Arrest**

| Group | mRS ≤3 | Unadjusted | Model 1 | Model 2 |
|-------|--------|------------|---------|---------|
| Good-quality CPR (80–120 compressions/min and 4–6 cm depth) |
| All (n=929) | | | | |
| Active (n=470) | 11.9% | 1.69 [1.08, 2.64] | 1.79 [1.10, 2.91] | 1.85 [1.13, 3.02] |
| Sham (n=459) | 7.4% | Ref | Ref | Ref |
| Shockable rhythm (n=346) | | | | |
| Active (n=177) | 28.3% | 1.69 [1.02, 2.79] | 1.68 [1.00, 2.81] | 1.77 [1.05, 2.99] |
| Sham (n=169) | 18.9% | Ref | Ref | Ref |
| Poor-quality CPR (<80 or >120 compressions/min and <4 or >6 cm depth) |
| All (n=202) | | | | |
| Active (n=87) | 4.6% | 0.46 [0.14, 1.48] | 0.40 [0.11, 1.41] | 0.47 [0.13, 1.75] |
| Sham (n=115) | 9.6% | Ref | Ref | Ref |

Odds ratios [95% confidence interval] are shown for unadjusted, Model 1 and Model 2. Odds ratio >1 indicates that active ITD confers a better outcome (mRS ≤3) than sham ITD. Model 1: adjusted for age, sex (and initial rhythm for all patients); and Model 2: adjusted for age, sex (and initial rhythm for all patients), bystander CPR, time from dispatch to first EMS arrival. mRS, modified Rankin Scale score. Other abbreviations as in Table 1.

**Table 4. Effect of CPR Quality on Survival to Hospital Discharge With Favorable Neurological Function in Subjects With a Witnessed Arrest**

| Group | mRS ≤3 | Unadjusted | Model 1 | Model 2 |
|-------|--------|------------|---------|---------|
| Good-quality CPR (90–110 compressions/min and 4–6 cm depth) |
| All (n=632) | | | | |
| Active (n=315) | 14.6% | 2.41 [1.40, 4.14] | 2.70 [1.49, 4.87] | 2.99 [1.62, 5.53] |
| Sham (n=317) | 6.6% | Ref | Ref | Ref |
| Shockable rhythm (n=240) | | | | |
| Active (n=123) | 33.3% | 2.43 [1.32, 4.46] | 2.52 [1.35, 4.70] | 2.90 [1.50, 5.59] |
| Sham (n=117) | 17.1% | Ref | Ref | Ref |
| Poor-quality CPR (<90 or >110 compressions/min and <4 or >6 cm depth) |
| All (n=390) | | | | |
| Active (n=190) | 5.3% | 0.53 [0.23, 1.17] | 0.52 [0.22, 1.20] | 0.62 [0.263, 1.49] |
| Sham (n=200) | 9.5% | Ref | Ref | Ref |

Odds ratios [95% confidence interval] are shown for unadjusted, Model 1 and Model 2. Odds ratio >1 indicates that active ITD confers a better outcome (mRS ≤3) than sham ITD. Model 1: adjusted for age, sex (and initial rhythm for all patients); and Model 2: adjusted for age, sex (and initial rhythm for all patients), bystander CPR, time from dispatch to first EMS arrival. Abbreviations as in Tables 1,3.

Next, these data were used to identify the optimal rate and depth needed to maximize survival with favorable neurological function during CPR with the sham and active ITD. Contour plots were generated for all survivors with favorable neurological function among those with a sham vs. active ITD. Most of the survivors in both groups received compression at rates between 80 and 120 per min with a depth of 4–6 cm. Survival with favorable neurological function was ‘more highly concentrated’ in the group with CPR plus active ITD treatment, with a readily identifiable “sweet spot” for rate and depth. Using numerical optimization techniques, the optimal rate and depth were determined to be 109 compressions per min and 4.5 cm for the sham ITD, and 106 compressions per min and 4.7 cm for the active ITD, respectively.

To further explore the importance of CPR quality on outcome, the outcomes of all witnessed arrests were examined independent of CPR quality as a secondary endpoint. There were no significant differences in witnessed OHCA outcomes between the active ITD (9.7%) vs. sham (9.5%) when the quality of CPR was not taken into consideration in the analysis (P=0.78). In addition, hospital discharge rates with favorable neurological function in witnessed arrests using a compression rate of 100–120 per min and a depth of 4–6 cm, the recommended rate and depth based on consensus of experts in the 2015 AHA Guidelines, were examined. Based on these guidelines, subjects with a witnessed arrest treated with a sham device would have an overall survival with good neurological outcome of 9.0% (23/256) vs. 12.4% (34/275) for the active ITD group (P=0.20).

**Discussion**

Recent studies have demonstrated a clinically important and statistically significant interaction between the quality of CPR...
potential benefit when CPR was performed correctly according to the AHA Guidelines in patients with a witnessed cardiac arrest. This focus on the witnessed arrest population reduced the uncertainty and variability in time between arrest and the start of CPR in unwitnessed cardiac arrest. Results from the present analysis demonstrated survival to hospital discharge with favorable neurological function as defined by a modified Rankin Scale score (mRS) ≤3 on the Z axis. (A) Plot of all survivors with known compression rate and depth treated with a sham impedance threshold device. (B) Plot of all survivors with known compression rate and depth treated with an active impedance threshold device.

Figure 3. Contour plots of proportion of survivors with favorable neurological function as defined by a modified Rankin Scale score ≤3 in each rate (compression per min: cpm)×depth (cm) cell. (A) Sham impedance threshold device treatment contour plot. The optimal rate was 109 cpm and the optimal depth was 4.5 cm. (B) Active impedance threshold device treatment contour plot. The optimal rate was 106 cpm and the optimal depth was 4.7 cm.

delivered and patient outcome, including assessment of CPR devices such as the ITD.2,3,8 When CPR quality is highly variable, the potential beneficial effects of adjunct devices may not be demonstrable.8,9 The current study focused on a reassessment of the use of the ITD, previously shown by one large randomized clinical trial to have no benefit,9 to determine its potential benefit when CPR was performed correctly according to the AHA Guidelines in patients with a witnessed cardiac arrest. This focus on the witnessed arrest population reduced the uncertainty and variability in time between arrest and the start of CPR in unwitnessed cardiac arrest. Results from the present analysis demonstrated survival to hospital discharge with
favorable neurological function was 11.9% with high-quality CPR and an active ITD vs. 7.4% with high-quality CPR and a sham device regardless of the first recorded heart rhythm. The active ITD was neither beneficial nor harmful when used on patients receiving poor-quality CPR defined as outside the AHA treatment recommendations. These new findings give an important insight into ways to significantly improve outcomes after OHCA. Contrary to the primary conclusion of the prospective randomized trial, the current results using the same database demonstrated that overall survival with good brain function could be improved by almost 60% in witnessed arrest patients, as shown in Table 3, simply by following the 2015 AHA Guidelines and using an active ITD.

Rationale of Need for CPR Quality Control
This study also highlighted some of the current challenges of CPR research. There were significant unrecognized CPR quality control issues in the ROC PRIMED study that have been more recently described.2–3 Chest compression rates were often excessive and the depth was often insufficient. The wide range of CPR quality in the ROC PRIMED study limits the interpretation of the original primary study endpoint results.2–3 However, these new results indicate a way for those able to implement high-quality CPR with the ITD to significantly improve outcomes after cardiac arrest. Both high-quality CPR, which may require real-time feedback or an automated CPR device, and the active ITD are needed to achieve this favorable outcome. It is noteworthy that the benefits of the active ITD were observed if the 2005 AHA Guidelines are followed, which was integral to the present study protocol, as well as the new 2015 AHA and ILCOR Guidelines.4 However, the effectiveness of the active ITD was the greatest with a compression rate of 106 per min and a depth of 4.7 cm.

The current findings help close two gaps in knowledge that were identified by the 2015 ILCOR.33 The first is the optimal compression rate for CPR with and without the ITD. In the present study the optimal rate was identified for both the sham (109 compressions per min) and the active ITD (106 compressions per min). These findings have significant implications for the optimal performance of conventional manual CPR with and without use of the ITD. For the first time, the rate and depth that should be used to optimize survival with favorable brain function after cardiac arrest have been shown. Rescuers can and should target this rate in patients with a witnessed cardiac arrest undergoing conventional CPR with and without an ITD. The second gap relates to the independent effect of the ITD and active compression-decompression (ACD) CPR. The current analysis demonstrated the clinical benefit of the ITD, without ACD CPR, as long as high-quality CPR is performed. As shown in Table 4 and Figure 3, this benefit is substantial; more than twice as many patients survived a witnessed cardiac arrest if compression was performed with a targeted rate of 105–110 per min and a depth of 4.5–5.0 cm. The new findings help provide guidance on how the ITD can be used to increase the number of patients who would likely survive with favorable neurological function after cardiac arrest.

Like any other medical intervention, if the intervention is not performed correctly, then it is difficult to observe and measure a potential benefit or harm from that intervention. CPR medical device trials involving closed-chest manual CPR, such as the ROC PRIMED study, one of the largest CPR trials ever performed, are dependent on CPR quality and thus inherently limited when the quality of CPR is variable. Similar to a vaccine that requires refrigeration and correct administration to remain effective, the ITD requires proper administration with high-quality CPR to be effective. Data from the current study demonstrate that the ITD cannot make poor CPR better, but that outcomes with high-quality CPR can be further improved by application of the active ITD.

Mechanophysiology of CPR and the ITD
The new findings from this ROC data re-analysis make sense physiologically, are consistent with recent studies of conventional CPR or ACD+ITD CPR, and have important clinical implications.34–35 The small negative intrathoracic pressure generated within the thorax during the chest wall recoil phase is critical for refilling the heart during the decompression phase of CPR.1 If chest compressions are not deep enough then chest recoil can be impaired.36 It has recently been demonstrated that when compressions are too rapid, the compression depth is too shallow. Inadequate compression depth reduces the natural recoil.37–39 The ITD cannot function to enhance negative intrathoracic pressure during the decompression phase of CPR without adequate chest wall recoil. By contrast, when CPR is performed according to AHA and ILCOR recommendations, using either both hands or an ACD CPR device, the addition of the ITD provides important hemodynamic and survival benefits.12,15–17,27–29,40

As with many physiological or mechanical systems, there is an optimal efficiency of the system that depends upon the components of the system. The ITD was tested in animals during CPR at a rate of 100 compressions per min and a depth of 20–25% of the anteroposterior diameter of their chest and found to double the cardiac perfusion and improve cerebral perfusion.8,18,23 In the current analyses, there was a distinct resonance peak in the CPR frequency plot, as shown in Figure 2. These analyses demonstrated the large potential benefit from use of an active ITD with high-quality CPR, performed according to the AHA Guidelines when the ROC PRIMED study was conducted. The study further demonstrated the potential benefit of using CPR feedback and monitoring tools to optimize the quality of CPR to ensure that it is performed with an average compression rate of 105–110 per min at the appropriate depth and with full chest wall recoil. These findings, for the first time, identify the “sweet-spot” for neurologically-sound survival after cardiac arrest and provide a roadmap to significantly improving survival for all subjects with a witnessed cardiac arrest.

The implications for these new findings in Japan could be substantial. At present the ITD is not commonly used in patients in cardiac arrest. It is, however, approved for sale by the Pharmaceutical and Medical Device Agency of Japan. It is important that if the ITD is implemented in Japan, it is used concurrently with CPR performed at a rate and depth similar to what has been reported herein, and that outcomes are tracked and reported in the future.

Study Limitations
The current study is limited by its post-hoc analysis of the initial ROC PRIMED study. One a priori assumption in the original ROC PRIMED study was that high-quality CPR would continue to be performed once sites qualified for the pivotal study phase. Ultimately, the ROC PRIMED study was suspended by the Data Safety Monitoring Board for futility. In view of the importance of quality CPR in the ROC PRIMED study, as shown by Idri et al and other ROC investigators,49 all subjects for whom compression rate and depth data were available were intentionally included in the current analysis. The primary analysis was further limited to subjects with a witnessed arrest to reduce background noise from those patients...
with unknown and frequently prolonged periods of untreated arrest. Thus the focus was on whether or not there was a potential benefit of the active ITD when high-quality CPR was utilized, as previously shown in animals, bench testing, humans, and computer models. Consequently, the current study analyses provide a way to estimate the benefit of the combination of high-quality CPR and the active ITD.

An important second limitation is that the current analysis could not take into account the potential interactions between the Analyze Early vs. Analyze Late interventions performed concurrently with investigation of sham and active ITD use in the ROC PRIMED study. The Analyze Early/Analyze Late data were not contained in the database available for the current analysis. In the main ROC PRIMED study analysis by Stiell et al, there appeared to be a potential benefit when the active ITD was used in subjects who were treated with 3 min of CPR prior to the first shock. It can be speculated that the theoretically harmful effects caused by poor-quality CPR delivered for shorter and longer periods of time may have contributed to some of the observations.

Conclusions

First responders inside and outside the hospital should focus on delivering high-quality conventional CPR with an average compression rate of 105–110 per min and an average depth of 4.5–5.0 cm and, when available, use an active ITD from the very start of CPR. This approach is supported by the current data analysis and previous studies showing that the combination of high-quality CPR and an active ITD can significantly improve outcomes for those experiencing a cardiac arrest.

Based on the current analysis, widespread use of the combination of high-quality CPR and an active ITD has the potential to save thousands of lives, especially of patients who have a witnessed arrest.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgments

This study was supported in part by the Toho University Joint Research Fund and JSPS KAKENHI (16K05591). The authors thank Dr Midori Yamada, Ms Misako Nakatani and Mrs Yuri Ichikawa for their assistance with the manuscript.

References

1. Kitamura T, Iwami T, Kawamura T, Nitta M, Nagao K, Nonogu H, et al. Nationwide improvements in survival from out-of-hospital cardiac arrest in Japan. Circulation 2012; 126: 2834–2843.

2. Stiell IG, Brown SP, Christenson J, Cheskes S, Nichol G, Powell J, et al. What is the role of chest compression depth during out-of-hospital cardiac arrest resuscitation? Crit Care Med 2012; 40: 1192–1198.

3. Idris AH, Guffey D, Aufderheide TP, Brown SP, Morrison LJ, Nichols P, et al. Relationship between chest compression rates and outcomes from cardiac arrest. Circulation 2012; 125: 3004–3012.

4. Yannopoulos D, McKenzie S, Aufderheide TP, Sigurdsson G, Pirrallo RG, Benditt D, 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: 363–372.

5. Aufderheide TP, Lurie KG. Death by hyperventilation: A common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med 2004; 32: S345–S351.

6. Abella BS, Sandbo N, Vassilatos P, Alvarado JP, O’Hearn N, Wigder HR, et al. Chest compression rates during cardiopulmonary resuscitation are suboptimal: A prospective study during in-hospital cardiac arrest. Circulation 2005; 111: 428–434.

7. Aufderheide TP, Pirrallo RG, Yannopoulos D, Klein JP, von Briesen C, Sparks CW, et al. Incomplete chest wall decompression: A clinical evaluation of CPR performance by EMS personnel and assessment of alternative manual chest compression-decompression techniques. Resuscitation 2005; 64: 353–362.

8. Yannopoulos D, Aufderheide TP, Abella BS, Duval S, Frascone RJ, Goodloe JM, et al. Quality of CPR: An important effect modifier in cardiac arrest clinical outcomes and intervention effectiveness trials. Resuscitation 2015; 94: 106–113.

9. Idris AH, Guffey D, Pepe PE, Brown SP, Brooks SC, Callaway CW, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. Crit Care Med 2015; 43: 840–848.

10. Edelson DP, Abella BS, Kramer-Johansen J, Wik L, Myklebust H, Barry AM, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. Resuscitation 2006; 71: 137–145.

11. Berg RA, Hemphill R, Abella BS, Aufderheide TP, Cave DM, Hazinski MF, et al. Part S: Adult basic life support. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122: S685–S705.

12. Aufderheide TP, Frascone RJ, Wayne MA, Mahoney BD, Swor RA, Dometier RM, 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: 301–311.

13. Lurie KG, Coffeen P, Shultz J, McKenzie S, Detloff D, Mulligan K. Improving active compression-decompression cardiopulmonary resuscitation with an inspiratory impedance valve. Circulation 1995; 91: 1629–1632.

14. Aufderheide T. A tale of seven EMS systems: An impedance threshold device and improved CPR techniques double survival rates after out-of-hospital cardiac arrest. Circulation 2007; 116: II-936–II-937.

15. Piaussane P, Soleil C, Lurie KG, Vicaut E, Duclos L, Payen D. Use of an inspiratory impedance threshold device on a facemask and endotracheal tube to reduce intrathoracic pressures during the decompression phase of active-compression-decompression cardiopulmonary resuscitation. Crit Care Med 2005; 33: 990–994.

16. Wolcke BB, Maurer DK, Schoeffermann MF, Teichmann H, Provo TA, Lindner KH, et al. 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. Circulation 2003; 108: 2201–2205.

17. Piaussane P, Lurie KG, Vicaut E, Martin D, Gueugniaud PY, Petit JL, et al. Evaluation of an impedance threshold device in patients receiving active compression-decompression cardiopulmonary resuscitation for out of hospital cardiac arrest. Resuscitation 2004; 61: 265–271.

18. Lurie KG, Mulligan KA, McKenzie S, Detloff D, Lindstrom P, Lindner KH. Optimizing standard cardiopulmonary resuscitation with an inspiratory impedance threshold valve. Chest 1998; 113: 1084–1090.

19. Lurie KG, Zielinski T, McKenzie S, Aufderheide T, Voelckel W. Use of an inspiratory impedance valve improves neurologically intact survival in a porcine model of ventricular fibrillation. Circulation 2002; 105: 124–129.

20. Hinchey PR, Myers JB, Lewis R, De Maio VJ, Reger E, Licatese D, et al. Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: The Wake County experience. Ann Emerg Med 2010; 56: 348–357.

21. Thigpen K, Davis SP, Basol R, Lange P, Jain SS, Olsen JD, et al. Implementing the 2005 American Heart Association guidelines, including use of the impedance threshold device, improves hospital discharge rate after in-hospital cardiac arrest. Respir Care 2010; 55: 1014–1019.

22. Aufderheide TP, Yannopoulos D, Lick CJ, Myers B, Romig LA, Stothert JC, et al. Implementing the 2005 American Heart Association Guidelines improves outcomes after out-of-hospital cardiac arrest. Heart Rhythm 2010; 7: 1357–1362.

23. Lurie KG, Voelckel W, Piaussane P, Zielinski T, McKenzie S, Kor D, et al. Use of an inspiratory impedance threshold valve during cardio-pulmonary resuscitation: A progress report. Resuscitation 2000; 44: 219–230.

24. Lurie KG, Yannopoulos D, McKenzie SH, Herman ML, Idris AH, Nadkarni VM, et al. Comparison of a 10-breaths-per-minute versus a 2-breaths-per-minute strategy during cardiopulmonary resuscitation in a porcine model of cardiac arrest. Resuscitation 2008; 73: 862–870.
2132

SUGIYAMA A et al.

25. Lurie KG, Zielinski T, McKnite S, Sukhum P. Improving the efficiency of cardiopulmonary resuscitation with an inspiratory impedance threshold valve. *Crit Care Med* 2000; 28: N207–N209.

26. Sugiyama A, Lurie KG, Maeda Y, Satoh Y, Imura M, Hashimoto K. Utilization of a model lung system to assess the effects of an inspiratory impedance threshold valve on the relationship between active decompression and intra-thoracic pressure. *Resuscitation* 1999; 42: 231–234.

27. Plaisance P, Lurie KG, Payen D. Inspiratory impedance during active compression-decompression cardiopulmonary resuscitation: A randomized evaluation in patients in cardiac arrest. *Circulation* 2000; 101: 989–994.

28. Pirrallo RG, Auffderheide TP, Provo TA, Lurie KG. Effect of an inspiratory impedance threshold device on hemodynamics during conventional manual cardiopulmonary resuscitation. *Resuscitation* 2005; 66: 13–20.

29. Lick CJ, Auffderheide TP, Niskanen RA, Steinkamp JE, Davis SP, Nygaard SD, et al. Take Heart America: A comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. *Crit Care Med* 2011; 39: 26–33.

30. Auffderheide TP, Nichol G, Rea TD, Brown SP, Leroux BG, Pepe PE, et al. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *Circulation* 2010; 122: S298 – S324.

31. Fried DA, Leary M, Smith DA, Sutton RM, Niles D, Herzberg DL, et al. The prevalence of chest compression leaning during in-hospital cardiopulmonary resuscitation. *Resuscitation* 2011; 82: 1019–1024.

32. Zuercher M, Hilwig RW, Ranger-Moore J, Nysaether J, Nadkarni VM, Berg MD, et al. Leaning during chest compressions impairs cardiac output and left ventricular myocardial blood flow in piglet cardiac arrest. *Crit Care Med* 2010; 38: 1141–1146.

33. Fitzgerald KR, Babbs CF, Frissora HA, Davis RW, Silver DI. Cardiac output during cardiopulmonary resuscitation at various compression rates and durations. *Am J Physiol* 1981; 241: H442 – H448.

34. Kern KB. Usefulness of cardiac arrest centers: Extending lifesaving post-resuscitation therapies: The Arizona experience. *Circ J* 2015; 79: 1156 – 1163.

35. Hifumi T, Kuroda Y, Kawakita K, Sawano H, Tahara Y, Hase M, et al. Effect of admission Glasgow coma scale motor score on neurological outcome in out-of-hospital cardiac arrest patients receiving therapeutic hypothermia. *Circ J* 2015; 79: 2201 – 2208.

36. Sayre MR, Koster RW, Botha M, Cave DM, Ciearkin MT, Handley AJ, et al. Part 5: Adult basic life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2010; 122: S298 – S324.

37. Fried DA, Leary M, Smith DA, Sutton RM, Niles D, Herzberg DL, et al. The prevalence of chest compression leaning during in-hospital cardiopulmonary resuscitation. *Resuscitation* 2011; 82: 1019–1024.

38. Zuercher M, Hilwig RW, Ranger-Moore J, Nysaether J, Nadkarni VM, Berg MD, et al. Leaning during chest compressions impairs cardiac output and left ventricular myocardial blood flow in piglet cardiac arrest. *Crit Care Med* 2010; 38: 1141–1146.

39. Fitzgerald KR, Babbs CF, Frissora HA, Davis RW, Silver DI. Cardiac output during cardiopulmonary resuscitation at various compression rates and durations. *Am J Physiol* 1981; 241: H442 – H448.

40. Frascone RJ, Wayne MA, Swor RA, Mahoney BD, Domeier RM, Olinger ML, et al. Treatment of non-traumatic out-of-hospital cardiac arrest with active compression decompression cardiopulmonary resuscitation plus an impedance threshold device. *Resuscitation* 2013; 84: 1214 – 1222.

41. Babbs CF. Effects of an impedance threshold device upon hemodynamics in standard CPR: Studies in a refined computational model. *Resuscitation* 2005; 66: 335 – 345.

42. ResQPR System. Instructions for Use. FDA, 2015. http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110024c.pdf (accessed April 27, 2015).

Supplementary Files

Supplementary File 1

Methods

Figure S1. How to use an impedance threshold device (ITD).

Figure S2. Mechanophysiology of cardiopulmonary resuscitation (CPR) with an impedance threshold device (ITD).

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-16-0449