Active Compression-Decompression Resuscitation and Impedance Threshold Device for Out-of-Hospital Cardiac Arrest: A Systematic Review and Metaanalysis of Randomized Controlled Trials*

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Objective: Active compression-decompression resuscitation and impedance threshold device are proposed to improve survival of patients of cardiac arrest by lowering intrathoracic pressure and increasing cardiac output. The results of clinical studies of active compression-decompression resuscitation or impedance threshold device were controversial. This metaanalysis pooled results of randomized controlled trials to examine whether active compression-decompression resuscitation or impedance threshold device would improve outcomes of out-of-hospital cardiac arrest in comparison with standard cardiopulmonary resuscitation and to explore factors modifying these effects.

Data Sources: Medline and Embase were searched from inception to September 2013.

Study Selection: Randomized controlled trials comparing active compression-decompression resuscitation or impedance threshold device with standard cardiopulmonary resuscitation in out-of-hospital cardiac arrest patients were selected. There were no restrictions for language, population, or publication year.

Data Extraction: Data on study characteristics, including patients, intervention details, and outcome measures, were independently extracted.

Data Synthesis: Fifteen trials, including 16,088 patients, were identified from 331 potentially relevant references. Return of spontaneous circulation was designated as the primary outcome. The pooled result showed no significant improvement in return of spontaneous circulation by active compression-decompression resuscitation or impedance threshold device in comparison with standard cardiopulmonary resuscitation (risk ratio, 1.04; 95% CI, 0.93–1.16; I^2, 46%). There was also no significant difference in survival or neurologic outcome at hospital discharge between active compression-decompression resuscitation or impedance threshold device and standard cardiopulmonary resuscitation. The meta-regression indicated that this minimal effect might be modified by two important prognostic factors, that is, witnessed status and response time. After adjustment of these two factors, impedance threshold device appeared to improve return of spontaneous circulation, which could be further augmented by advanced airway use.

Conclusions: Active compression-decompression resuscitation or impedance threshold device seemed not to improve return of spontaneous circulation in out-of-hospital cardiac arrest patients. The meta-regression indicated two probable prognostic factors causing this minimal effect. Nonetheless, these findings referred to differences between trials and could not necessarily be extrapolated to individual patients. The individual patient-level extrapolation may need to be solved by a future randomized controlled trial. (*Crit Care Med* 2015; 43:889–896)

Key Words: cardiopulmonary resuscitation; critical care; emergency medical service; emergency medicine; heart arrest; metaanalysis

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Out-of-hospital cardiac arrest (OHCA) is a clinical condition still characterized by a poor prognosis (1). High-quality cardiopulmonary resuscitation (CPR) with complete chest recoil is addressed in 2010 American Heart Association guidelines (2). However, standard cardiopulmonary resuscitation (STR), defined as manual chest compressions with rescue breathing, is inherently inefficient (3). The use of active compression-decompression resuscitation (ACDR) or impedance threshold device (ITD) was proposed to improve CPR efficiency.

With the use of a hand-held device with a suction cup, ACDR is performed to lower the intrathoracic pressure by active chest decompression and thereby augment the venous return. Experimental studies on animal models of cardiac arrest have shown that ACDR was associated with a higher rate of return of spontaneous circulation (ROSC) than STR (4). Clinical studies, however, showed inconsistent results. A Cochrane metaanalysis concluded that ACDR might not be superior to STR (5).

ITD, a valve device used to reduce air entry into lungs during chest decompression, is proposed to produce a similar effect as ACDR by maintaining negative intrathoracic pressure during CPR (6). A metaanalysis demonstrated that ITD improved ROSC and early survival (7). However, this analysis included a trial comparing ACDR/ITD with STR (8), of which the observed benefit might not be totally ascribed to ITD alone.

The clinical evidence for the effect of ACDR or ITD in OHCA was conflicting (9, 10). This metaanalysis quantitatively pooled the results of randomized controlled trials (RCTs) to examine whether use of ACDR or ITD would improve outcomes of OHCA in comparison with STR and explore whether other factors would modify the effects of these devices.

MATERIALS AND METHODS

Data Sources and Searches

We performed this metaanalysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (11). Two authors (C.-H.W., C.-C.L.) independently searched Medline and Embase from inception to September 2013 according to a prespecified protocol. The search terms included "active compression-decompression," "impedance threshold device," "cardiac arrest," and "cardiopulmonary resuscitation." There were no restrictions on language, population, or publication year. We did not search abstracts from conferences, proceedings, or clinical trial registries. Instead, we manually reviewed the bibliographies of relevant studies, reviews, and metaanalyses to identify references we may have missed during our primary search. The authors of the included trials were contacted for missing information, if necessary. This study was reviewed by the local institutional review board and is exempt from requiring approval.

Study Selection

Two authors (C.-H.W., M.-S.T.) independently scanned the titles and abstracts of all retrieved articles and selected those that were pertinent to this review. The following prespecified inclusion criteria were used: 1) being an RCT, 2) comparisons were made between the use of ACDR or ITD and STR in OHCA, and 3) the results included ROSC, survival, or neurologic outcome. If studies shared the same cohort, the study with more patients was selected into analysis.

After retrieving full articles of potentially relevant trials, two reviewers (C.-H.W., M.-S.T.) independently assessed each study's eligibility on the basis of the inclusion criteria and settled differing opinions by consensus or consultation with a third investigator (W.-J.C.).

Data Extraction and Quality Assessment

Four authors independently extracted data by using a prespecified protocol (W.-T.C., C.-H.H., M.H.-M.M., C.-C.F.). Each trial was reviewed independently by two of these four authors to ensure the correctness of the extracted data, which included 1) study design, 2) study population characteristics, 3) details of interventions, and 4) types of outcomes measured.

ROSC was prespecified as the primary outcome in the analysis. Other prespecified secondary outcomes included survival for 24 hours, survival to hospital discharge, and satisfactory neurologic outcome at hospital discharge.

The Cochrane risk of bias tool was adopted to assess the risk of bias for each RCT (12). Each RCT was scored as "high risk," "low risk," or "unclear" with respect to random sequence generation, allocation concealment, blinding process, incomplete outcome data, and selective reporting (12). Discrepancies in assessment were resolved through discussions between the extraction authors or consultation with the supervising investigator (S.-C.C.).

Data Synthesis and Analysis

Metaanalysis and meta-regression were performed using the rmeta and metafor packages in the R 2.15.3 software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p value of less than 0.05 was considered statistically significant. The estimated risk ratio (RR) and the 95% CIs of each individual study were recorded for computing the pooled (i.e., weighted averaged) estimate of effect size from all collected studies. The response variable to be analyzed in metaanalysis and meta-regression was the transformed "log(RR)" for a more symmetric response distribution.

Metaanalysis was conducted first. Heterogeneity in the estimated RRs between individual studies was examined using 1) the I^2 statistic, in which I^2 more than 40% indicated a substantial level of heterogeneity, and 2) the test of heterogeneity, in which p value of less than 0.05 indicated heterogeneity. If heterogeneity was not evident, fixed-effects summary estimates (Mantel-Haenszel method) were reported in forest plots; otherwise, random-effects summary estimates (DerSimonian-Laird method [13]) were reported.

If significant statistical heterogeneity was found between individual studies in metaanalysis, subgroup analysis was performed by stratifying collected studies according to the interventions (ACDR or ITD) used in experimental groups. Next, to account for the heterogeneity, meta-regression was performed with potentially relevant covariates (listed in **Table 1**) as moderators. The stepwise variable selection procedure (with iterations between the forward and backward steps) was applied to obtain the final regression model. All the univariate significant/

TABLE 1. Characteristics of the Included Randomized Controlled Trials

Study	Year	*n*	Country	Mean Age/ Male %	Witnessed Cardiac Arrest %	Bystander Cardio-pulmonary Resuscitation %	Response Time	Initial Arrest Rhythm (Shockable Rhythm/ Pulseless Electrical Activity/ Asystole %)	ITD Attach-ment Site (Endotracheal Tube/ Advanced Airways %)
ACDR vs STR									
Lurie et al (17)	1994	130	United States	67.1/71.5	68.5	36.9	3.4	61.5/25.4/13.1	NA
Schwab et al (18) (Fresno)	1995	253	United States	64.5/61.3	61.3	33.6	4.9	32.8/17.8/42.3	NA
Schwab et al (18) (San Francisco)	1995	607	United States	65.5/67.1	52.6	18.1	3.95	22.5/36.6/40.9	NA
Luiz et al (19)	1996	56	Germany	68.9/73.2	73.2	30.4	6	26.8/17.8/55.4	NA
Mauer et al (20)	1996	220	Germany	68.8/NA	68.6	15.5	7.2	45/34.1/20.9	NA
Stiell et al (21)	1996	1,011	Canada	68/63.6	59.2	19.6	NA	32.5/21.9/41.3	NA
Goralski et al (22)	1998	145	France	61.6/73.1	81.5	22.4	16.5	20.7/3.4/75.9	NA
Mauer et al (23)	1998	120	Germany	68.3/NA	69.2	8.3	7.65	45.2/34.1/20.8	NA
Nolan et al (24)	1998	576	United Kingdom	67.2/68.4	70.3	32.5	6.5	60.2/14.6/25.2	NA
Plaisance et al (16)	1999	750	France	58.5/68	73.9	7.6	NA	12.5/6/82	NA
Skogvoll and Wik (25)	1999	302	Norway	71/73	81.5	57.4	9	57/NA/NA	NA
STR/ITD vs STR									
Aufderheide et al (26)	2005	230	United States	65.5/61.3	58.7	22.2	4.7	25.7/22.6/50.9	NA/NA
Pirrallo et al (27)	2005	22	United States	61.2/59.1	45.5	22.7	8.7	18.2/31.8/45.5	100/100
Aufderheide et al (9)	2011	8,718	United States/ Canada	66.9/64.6	48.7	38.5	5.8	24.5/23.9/44.2	76.2/86.9
ACDR/ITD vs STR									
Wolcke et al (8)	2003	210	Germany	67/61.9	74.8	24.3	5.95	40/29.5/30.5	100/100
Frascone et al (15)	2013	2,738	United States	63.8/62.4	54.6	40.8	6.6	25.1/23.5/50	NA/86.7

ITD = impedance threshold device, ACDR = active compression-decompression resuscitation, STR = standard cardiopulmonary resuscitation, NA = not applicable.

nonsignificant covariates and some of their interaction terms (including ACDR × ITD and ITD × response time) were put on the variable list to be selected. The significance levels for entry and for stay were set to 0.15 (or larger) for being conservative. With the aid of substantive knowledge, the final regression model was identified manually by dropping the covariates with *p* value of more than 0.05 one at a time until all regression coefficients were statistically significant. Generalized additive models were fitted to detect nonlinear effects of continuous covariates and identify appropriate cutoff point(s) for dichotomizing a continuous covariate, if necessary, during the stepwise variable selection procedure.

In meta-regression, if the test of residual heterogeneity was not statistically significant, the result of a fixed-effects meta-regression model was reported; otherwise, that of mixed-effects meta-regression model with the Knapp and Hartung adjustment was reported instead. The potential publication bias was examined by funnel plot.

RESULTS

Search Results and Description

The review process is shown in **Figure 1**. Two trials (10, 14) were excluded because more patients were enrolled from the

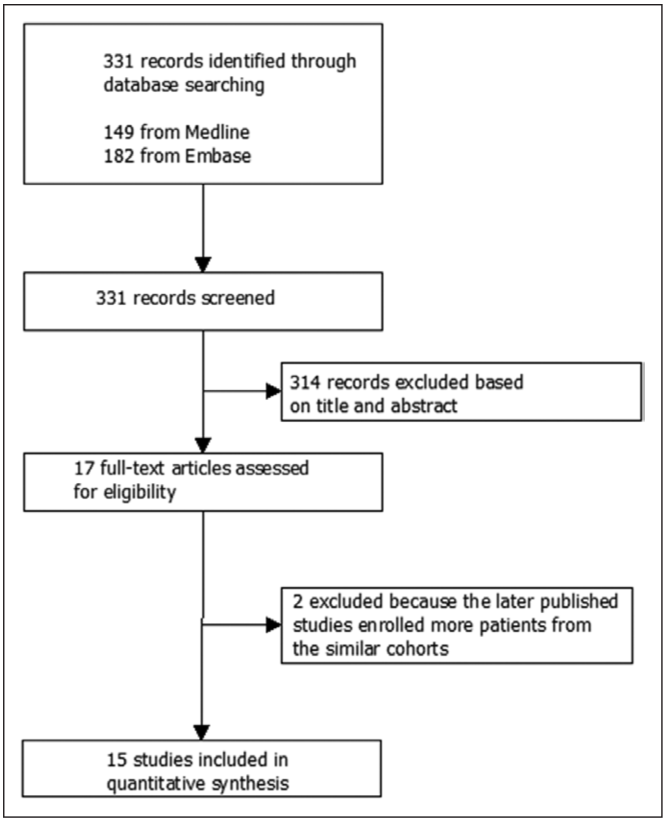

Figure 1. Flow diagram of the literature search. The literature search process was shown. Two studies were excluded after full-text review because more patients were enrolled from similar cohorts in later published trials.

similar cohorts in later published trials (15, 16). We identified 15 RCTs (8, 9, 15–27) including 16,088 patients for metaanalysis (Table 1). According to interventions in experimental groups, the included RCTs were categorized into three subgroups: ACDR versus STR, STR/ITD versus STR, and ACDR/ITD versus STR. The trial by Schwab et al (18) provided data of two cities, which were reported separately. The trial by Stiell et al (21) enrolled patients of OHCA and in-hospital cardiac arrest; only the data of OHCA were presented.

Patients with noncardiac causes of arrest were excluded in six trials (8, 20, 23, 25–27). Patients were excluded from trials if the delay between cardiac arrest and basic CPR exceeded 15 minutes in three trials (8, 9, 21) and 30 minutes in another three trials (16, 22, 24). In most trials, the response time from dispatch to the arrival of first emergency medical service (EMS) team (either basic life support or advanced life support team) was within 10 minutes. Two trials provided time from collapse to EMS arrival instead, which were 5.1 minutes (21) and 9.2 minutes (16), respectively. In trials involving ITD use, ITD was used with endotracheal tube (ETT) in two trials (8, 27), whereas in the other two trials (9, 15), ITD could be attached between the ventilation bag and a facemask or an advanced airway (e.g., supraglottic airways or ETT).

As shown in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B152), the blinding process could not be performed in trials involving ACDR. Several trials used alternating periods (day, week, or month) to allocate patients (clustered randomization) and showed a high risk of bias in allocation concealment (8, 16–18, 24). All trials were managed by intention-to-treat analysis with complete follow-up.

The outcomes are presented in **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/CCM/B153). The timing of ROSC recording was not defined in most trials, and the results were pooled together as ROSC before hospital admission. Goralski et al (22) reported survival to ICU discharge, which was classified as survival to hospital discharge. Modified Rankin scale of up to 3 (28) and Glasgow–Pittsburgh cerebral performance category score of up to 2 (29)

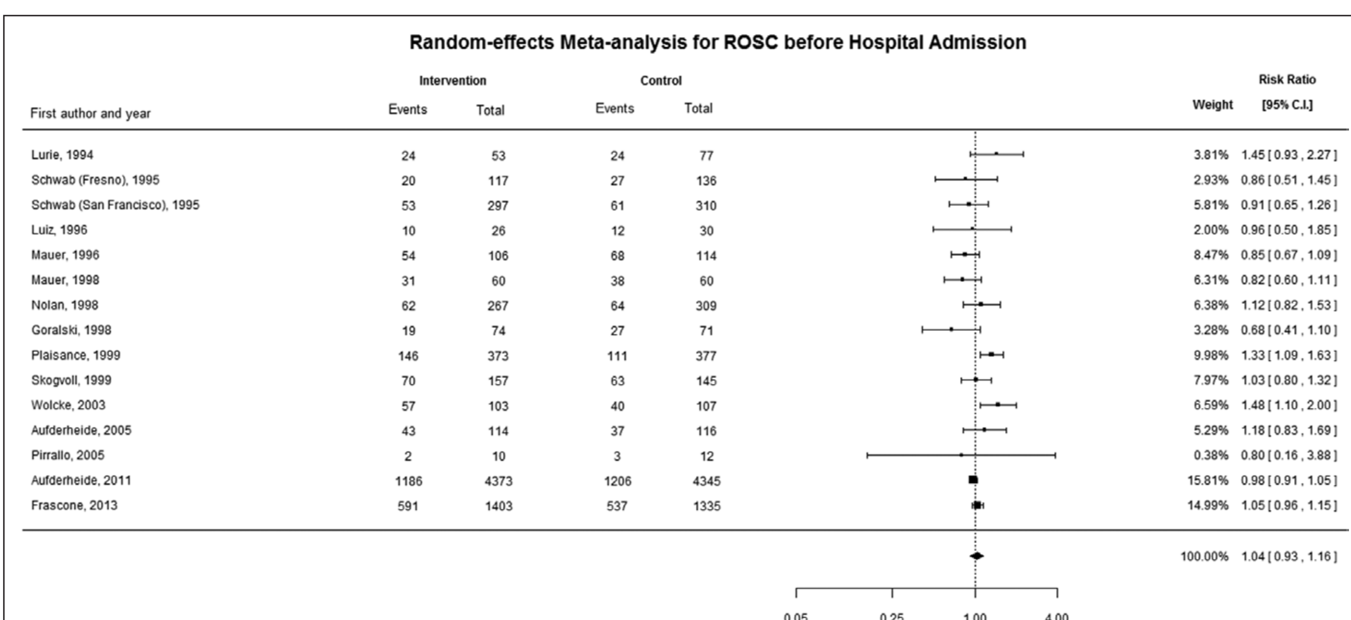

Figure 2. Forest plot of the summary effect estimates of return of spontaneous circulation (ROSC) before hospital admission. The comparison was made between use of active compression-decompression resuscitation or impedance threshold device (intervention) and standard cardiopulmonary resuscitation (control) in patients with out-of-hospital cardiac arrest.

were categorized as satisfactory neurologic outcomes (30). Lurie et al (17) reported the number of patients who were awake, alert, and oriented to person, place, and time, which was also counted as satisfactory neurologic outcome.

Quantitative Data Synthesis

There was no significant difference in ROSC between use of ACDR or ITD and STR (RR, 1.04; 95% CI, 0.93–1.16; I^2, 46%) (**Fig. 2**) (**Table 2**). There were also no differences in survival and neurologic outcomes in either main or subgroup analysis (Table 2).

In the meta-regression, when all covariates except ITD attachment site in **Table 3** were analyzed as independent variables with log(RR) of ROSC as the response variable, witnessed cardiac arrest ($p < 0.001$) and ITD use ($p = 0.002$) were noted to be positively associated with log(RR) of ROSC, whereas response time ($p = 0.004$) was inversely correlated with log(RR) of ROSC (**Table 4**). The general additive models plot demonstrated that log(RR) of ROSC would be higher when the response time was less than 6.5 minutes, which was used as the cutoff point (**Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/B154). When interaction terms of ACDR × ITD and ITD × response time (< 6.5 min) were put into meta-regression model, these two interaction terms were not statistically significant.

When ITD attachment site was considered, the meta-regression was restricted to only four studies involving ITD use (8, 9, 15, 27). Multivariate analysis was not performed because of the limited number of trials. The univariate analysis on ITD attachment site showed that advanced airway use was positively associated with log(RR) of ROSC ($p = 0.018$) in these four studies (Table 3). The funnel plot did not show obvious publication bias (**Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/CCM/B155).

DISCUSSION

Previous metaanalyses examined the effect of ACDR or ITD for OHCA separately (5, 7). The interaction among ACDR, ITD,

TABLE 2. Pooled Outcomes of the Included Randomized Controlled Trials

Outcomes	No. of Studies	Events/No. of Intervention	Events/No. of Control	Risk Ratio (95% CI)	I^2
Use of ACDR or ITD vs STR					
ROSC before hospital admission	14	2,368/7,533	2,318/7,544	1.04 (0.93–1.16)	46%
Survival for 24 hr	4	217/875	147/881	1.49 (1.24–1.79)	0
Survival to hospital discharge	12	663/7,537	622/7,549	1.07 (0.96–1.18)	0
Satisfactory neurologic outcome at hospital discharge	10	472/7,362	428/7,349	1.24 (0.93–1.65)	19%
ACDR vs STR					
ROSC before hospital admission	9	489/1,530	495/1,629	1.00 (0.86–1.16)	48%
Survival for 24 hr	2	93/447	63/448	1.12 (0.44–2.87)	78%
Survival to hospital discharge	9	122/1,658	119/1,762	1.11 (0.87–1.41)	0
Satisfactory neurologic outcome at hospital discharge	7	94/1,483	82/1,562	1.24 (0.93–1.65)	0
STR/ITD vs STR					
ROSC before hospital admission	3	1,231/4,497	1246/4,473	0.98 (0.92–1.05)	0
Survival for 24 hr	1	19/114	14/116	1.38 (0.73–2.62)	NA
Survival to hospital discharge	1	357/4,373	355/4,345	1.00 (0.87–1.15)	NA
Satisfactory neurologic outcome at hospital discharge	1	254/4,373	260/4,345	0.97 (0.82–1.15)	NA
ACDR/ITD vs STR					
ROSC before hospital admission	2	648/1,506	577/1,442	1.21 (0.86–1.69)	79%
Survival for 24 hr	1	38/103	24/107	1.64 (1.07–2.54)	NA
Survival to hospital discharge	2	184/1,506	148/1,442	1.19 (0.97–1.46)	0
Satisfactory neurologic outcome at hospital discharge	2	124/1,506	86/1,442	1.39 (1.06–1.81)	0

ACDR = active compression-decompression resuscitation, ITD = impedance threshold device, STR = standard cardiopulmonary resuscitation, ROSC = return of spontaneous circulation, NA = not applicable.

TABLE 3. Results of Univariate Meta-Regression Analysis on Log Relative Risk of Return of Spontaneous Circulation

Variable	Odds Ratio (95% CI)	*p*
Mean age	0.979 (0.960–0.997)	0.023
Male (%)	1.000 (0.982–1.018)	0.980
Studies of North America	0.942 (0.840–1.056)	0.304
Witnessed cardiac arrest (%)	1.004 (0.999–1.009)	0.086
Bystander cardiopulmonary resuscitation (%)	0.998 (0.994–1.003)	0.471
Average response time (min)	0.971 (0.936–1.006)	0.105
Initial shockable rhythm (%)	1.000 (0.995–1.004)	0.911
Use of active compression-decompression resuscitation	1.072 (0.977–1.177)	0.143
Use of ITD	0.993 (0.888–1.111)	0.905
ITD attachment site (% of advanced airways use)	1.028 (1.005–1.051)	0.018

ITD = impedance threshold device.

and other factors was less examined. The current metaanalysis demonstrated that use of ACDR or ITD, in comparison with STR, seemed not to improve survival and neurologic outcomes of OHCA. Nonetheless, this minimal effect might be confounded by two important prognostic factors, that is, witnessed status and response time. The meta-regression uncovered that if these factors were controlled, ITD could still be effective. Use of an advanced airway also seemed to augment ITD effect.

Laboratory research has demonstrated that blood flow is significantly increased by ACDR compared with STR (31, 32). The minimal effect of ACDR in OHCA observed in the subgroup analysis was consistent with the Cochrane metaanalysis (5). There were several explanations for this discrepancy between animal and clinical studies, such as the higher physical demand of ACDR in real practice (33) and the nonadherence to the chest of the ACDR device (17). The only study showing a survival benefit of ACDR was that by Plaisance et al (16), in which more staff were dispatched to perform ACDR, and with more experience in its use, as compared with other studies.

TABLE 4. Results of Multivariate Meta-Regression Analysis on Log Relative Risk of Return of Spontaneous Circulation

Variable	Odds Ratio (95% CI)	*p*
Witnessed cardiac arrest (%)	1.017 (1.008–1.027)	< 0.001
Average response time (min)	0.936 (0.895–0.978)	0.004
Use of impedance threshold device	1.366 (1.120–1.665)	0.002

ITD improved hemodynamics and neurologic outcomes in animal studies (34–36). In comparison with ACDR, ITD is relatively easy to use in clinical settings. A previous metaanalysis (7) indicated that ITD was effective in improving short-term survival in OHCA patients, but a study (8) comparing ACDR/ITD with STR was also included in the analysis. In current subgroup analysis, ITD seemed not to improve either short-term or long-term outcome. Nonetheless, the meta-regression uncovered that this minimal effect might be caused by two important prognostic factors for OHCA, that is, witnessed status and response time.

The meta-regression showed that higher proportion of witnessed cardiac arrest and shorter response time were associated with higher log(RR) of ROSC, consistent with findings of other studies (37). Basically, these two factors similarly implied that time factor seemed to influence the ITD effect significantly. The use of ITD might be most effective within the circulatory phase (4–10 min following collapse) (38) when chest compression was addressed. Although the interaction term of ITD × response time (< 6.5 min) was not statistically significant, the limited number of included RCTs might lead to this type II error. Some secondary studies (39, 40) of the Resuscitation Outcomes Consortium Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis trial also pointed out that certain important CPR metrics, such as perishock pause and chest compression rates, had significantly influenced the survival of patients in this large trial. These results suggested that some subgroup of patient might still benefit from the use of ITD. More importantly, it has been noted that the response time or witnessed status is a summary of patient characteristics rather than a specific attribute of the trial. The finding is an aggregated association that cannot necessarily be extrapolated to individual patients. The individual patient-level extrapolation may need to be solved by an RCT.

Animal studies have shown the superiority of the drop in intrathoracic pressure and the increase in cerebral perfusion when ACDR and ITD were used in combination in comparison with STR, ACDR alone, or ITD alone (41, 42). Current subgroup analysis did not reveal the probable synergistic effect of ACDR/ITD. In the meta-regression, the interaction term of ACDR × ITD was not statistically significant either. However, the limited number of RCTs studying ACDR/ITD combination might lead to this result.

The meta-regression indicated that advanced airway use might be synergistic with ITD. Most animal studies showing a survival benefit of ITD actually used ITD and ETT in combination rather than ITD with a facemask (34–36). The negative intrathoracic pressure might be better maintained by the occluded ventilation circuit with advanced airways. Plaisance et al (43) had demonstrated that the airway pressures with an ITD on either a facemask or ETT were similar in OHCA. Nonetheless, in their study (43), there was a trend showing that ITD with ETT could induce more negative pressure than ITD with a facemask, either in mean (–5.8 vs –3.4 mm Hg) or maximal pressure (–7.3 vs –4.6 mm Hg) (43).

Historically, effective use of facemask ventilation has been challenging even among skilled clinicians (44, 45). The single-handed "E–C" technique often tilts the facemask to the left, allowing air to leak under the right side of the mask (46). Plaisance et al (43) reduced this leak by using a strap around the head of the patient and by ventilating through a two-rescuer technique. Nonetheless, in most emergency services, the limited number of dispatched staff did not allow such a practice. In the subgroup analysis of the RCT by Aufderheide et al (9), there was also a nonsignificant trend in favor of ITD with ETT than with a supraglottic airway or a facemask in patients receiving STR. Nonetheless, there were only four RCTs included in this meta-regression model examining the effect of advanced airway use without other confounders controlled. Further studies should be conducted to examine this association.

In summary, despite that the pooled result indicated ACDR or ITD might not be effective in improving outcomes of OHCA patients, the meta-regression uncovered that time factor appeared to influence the ITD effect significantly. It might be difficult to shorten response time for every OHCA patient. Accordingly, this hypothesis might be examined in patients of in-hospital cardiac arrest, in whom the response time could probably be shorter and intubation could possibly be performed for every event although the etiology and confounding variables might be different from OHCA. ACDR has been examined in patients of in-hospital cardiac arrest; however, there are no similar studies for ITD (5).

Limitations

There was tremendous clinical and methodological heterogeneity among the included trials. Especially, the differences in EMS practice might make difficulties in shortening response time and limit the generalizability of this result. Prehospital intubation was not performed in most EMS cases. In some studies, prehospital intubation was viewed as a potentially harmful procedure for OHCA patients (47).

CONCLUSIONS

ACDR or ITD seemed not to improve ROSC in OHCA. This result might be confounded by two important prognostic factors, that is, witnessed status and response time. However, these hypotheses were based on aggregated association and might be better examined in future studies.

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