# Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomized trial

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## Introduction

- > 800,000 Europeans and North Americans have an out-of-hospital cardiac arrest every year, overall survival ≒ 5%.
  - Inefficient CPR
  - compromised haemodynamics

## Introduction

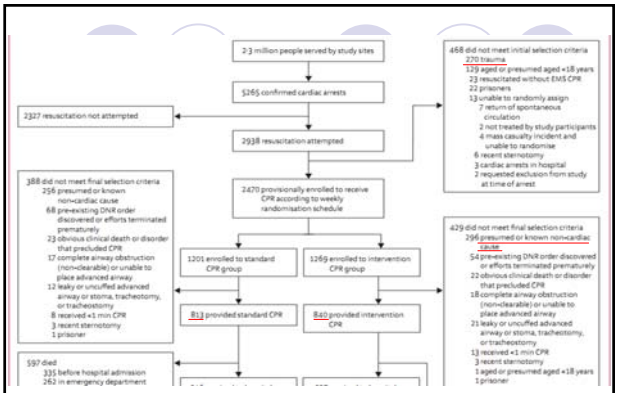
- Augmentation of negative intrathoracic pressure during the decompression phase
  - increase cardiac and cerebral perfusion
  - decrease intracranial pressure
- Clinical studies have also shown substantial improvement in 24-h survival with this approach.
- Cmbination of active compression decompression CPR(ACD-CPR) and an impedance-threshold device(ITD).

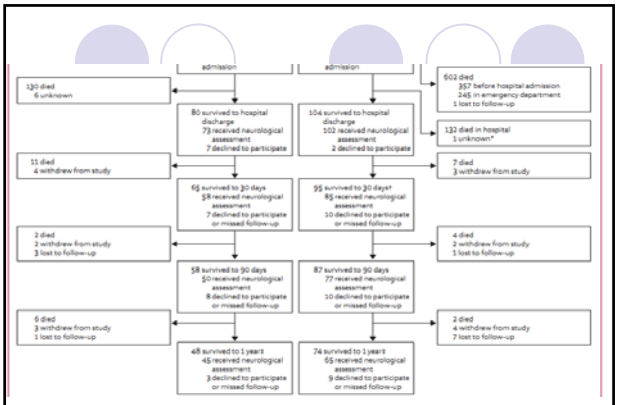
## Introduction

- We aimed to establish whether ACD-CPR plus a ITD would result in improved survival to hospital discharge with favourable neurological function, compared with standard CPR.

## Method

- Adults ( ≥18 years of age) with out-of-hospital cardiac arrest were eligible for the study
- Exclusion criteria
  - < 18 y/o
  - traumatic injuries
  - clinical death
  - in-hospital cardiac arrest
  - recent sternotomy
  - Unsuccesful intubation( tracheotomy, tracheostomy)
  - non-cardiac causes (pulmonary embolism, hemorrhage causes stroke, metabolic abnormalities, drug overdose, and electrocution )





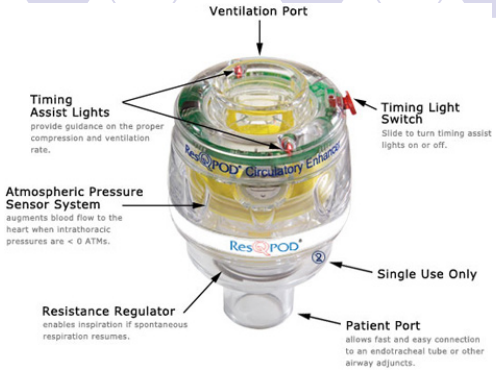
## Randomization and Masking

- independent biostatistician (RGH): to assign patients to receive standard CPR or study intervention in a one to one ratio

## Procedures:

- Standard CPR(30:2), defibrillation, advanced life support
- Intervention protocol: 80 compr./min with ACD force gauge puls ITD used to help achieve recommended compr. Depth.

## Impedance threshold device




## ACD (active compression decompression)

## Standard vs intervention CPR

## Baseline Patient Characteristics

| | Standard CPR group (n=813) | Intervention* group (n=840) |
|---|---|---|
| Mean age (years) | 66·8 (14·5) | 67·0 (15·2) |
| 18–34 | 12 (2%) | 11 (1%) |
| 35–44 | 36 (4%) | 47 (6%) |
| 45–54 | 114 (14%) | 133 (16%) |
| 55–64 | 215 (26%) | 179 (21%) |
| 65–74 | 172 (21%) | 169 (20%) |
| 75–84 | 162 (20%) | 192 (23%) |
| ≥85 | 102 (13%) | 109 (13%) |
| Sex (male) | 539 (66%) | 558 (66%) |
| Arrest surroundings | | |
| Witnessed before arrival of first responder | 383 (47%) | 398 (47%) |
| Witnessed after arrival of first responder | 76 (9%) | 80 (10%) |
| Unwitnessed | 353 (43%) | 361 (43%) |
| Data not available | 1 (<1%) | 1 (<1%) |
| Bystander CPR | | |
| Provided | 350 (43%) | 357 (43%) |
| Data not available | 1 (<1%) | .. |
| Initial recorded cardiac arrest rhythm | | |
| Ventricular fibrillation and pulseless ventricular tachycardia | 247 (30%) | 292 (35%) |
| Asystole | 379 (47%) | 375 (45%) |
| Pulseless electrical activity | 180 (22%) | 170 (20%) |
| Data not available | 7 (<1%) | 3 (<1%) |
| Emergency call to first response time (min) | 6·5 (3·3) | 6·4 (3·1) |

## Baseline Patient Characteristics

| | | |
|---|---|---|
| Emergency call to EMS CPR start time (min)† | 6·6 (3·4) | 6·7 (3·2) |
| Emergency call to placement of study devices† (min) | .. | 7·1 (3·5) |
| Impedance-threshold device airway attachment site | | |
| Facemask | .. | 717 (85%) |
| Endotracheal tube | .. | 586 (70%) |
| Supraglottic airway (eg, laryngeal mask airway, Combitube, King) | .. | 169 (20%) |
| Epinephrine dose (mg) | 3·3 (2·1) | 3·3 (2·1) |
| Patients without ROSC | 3·8 (1·9) | 3·8 (1·9) |
| Duration of CPR (min) | 27·6 (12·2) | 28·1 (11·4) |
| Patients without ROSC | 32·3 (9·5) | 32·3 (8·1) |
| ROSC during CPR before hospital admission | 324 (40%) | 343 (41%) |
| Enrolment site | | |
| 1 | 122 (15%) | 121 (14%) |
| 2 | 155 (19%) | 169 (20%) |
| 3 | 113 (14%) | 92 (11%) |
| 4 | 189 (23%) | 208 (25%) |
| 5 | 46 (6%) | 40 (5%) |
| 6 | 149 (18%) | 169 (20%) |
| 7 | 39 (5%) | 41 (5%) |
| Admitted to hospital | 216 (27%) | 237 (28%) |
| In-hospital hypothermia (% admitted) | 85 (39%) | 92 (39%) |
| Cardiac catheterisation (% admitted) | 72 (33%) | 100 (42%) |
| Coronary stenting (% admitted) | 28 (13%) | 38 (16%) |
| Coronary bypass surgery (% admitted) | 6 (3%) | 15 (6%) |
| Implanted cardiodefibrillator (% admitted) | 30 (14%) | 41 (17%) |

## Endpoints

- **Primary:**
  survival to hospital discharge with favorable neurological function, (MRS≦3)
- **Secondary safety endpoint:**
  assessed the rate of major adverse events until hospital discharge
  (death, cerebral bleeding, pul. edema, bl. requiring trasf.,. chest fr., int. thoracic & abd. inj….)

## Additional secondary effectiveness endpoints

- 90 and 365 days after out-of-hospital cardiac arrest
- Attention, short and long-term memory, judgment, spatial ability
- Functional disability (disability rating index, depression, emotional stability with Bech depression inventory)

## Primary and Secondary Endpoints

| | Standard CPR group (n=813) | Intervention* group (n=840) | p value |
|---|---|---|---|
| **Primary composite study endpoints** | | | |
| Modified Rankin scale score at hospital discharge† | | | 0·039 |
| 0 | 3 (<1%) | 11 (1%) | .. |
| 1 | 8 (1%) | 11 (1%) | .. |
| 2 | 26 (3%) | 30 (4%) | .. |
| 3 | 10 (1%) | 23 (3%) | .. |
| 4 | 10 (1%) | 9 (1%) | .. |
| 5 | 16 (2%) | 18 (2%) | .. |
| 6 | 727 (89%) | 734 (87%) | .. |
| Survival data for hospital discharge not available | 6 (<1%) | 2 (<1%) | .. |
| Survived, but data for MRS not available | 7 (<1%) | 2 (<1%) | .. |
| MRS ≤3 (primary study endpoint) | 47 (6%) | 75 (9%) | 0·019 |
| **Secondary survival endpoints** | | | |
| Survived to 24 h after arrest | 176 (22%) | 197 (24%) | 0·41 |
| Data not available | 9 (1%) | 6 (<1%) | .. |
| Survived to hospital discharge | 80 (10%) | 104 (12%) | 0·12 |
| Data not available | 6 (<1%) | 2 (<1%) | .. |
| Discharge location (% discharged) | | | |
| Home | 47 (59%) | 67 (64%) | 0·75 |
| Other | 28 (35%) | 35 (34%) | .. |
| Data not available | 5 (6%) | 2 (2%) | .. |
| Survived to 90 days | 58 (7%) | 87 (10%) | 0·029 |
| Data not available | 15 (2%) | 8 (1%) | .. |
| Survived to 1 year | 48 (6%) | 74 (9%) | 0·030 |
| Data not available | 19 (2%) | 19 (2%) | .. |
| Initial recorded arrest rhythm in patients with MRS ≤3 | | | |
| Ventricular fibrillation and pulseless ventricular tachycardia | 40 (17%) | 66 (23%) | 0·0645‡ |
| Asystole | 3 (<1%) | 6 (2%) | .. |
| Pulseless electrical activity | 3 (2%) | 2 (1%) | .. |
| Unknown | 1 (<1%) | 1 (<1%) | .. |
| **Neurological assessment** | | | |
| CASIS (patients with complete score, validity=1) | | | |
| 90 days | 93·2 (7·4) | 90·4 (13·4) | 0·251 |
| Data not available | 19 (33%) | 35 (40%) | .. |
| 365 days | 92·9 (12·0) | 94·5 (4·5) | 0·473 |
| Data not available | 16 (33%) | 32 (43%) | .. |
| Beck depression inventory score¶ | | | |
| 90 days | 4·8 (3·9) | 6·5 (6·8) | 0·098 |
| Data not available | 14 (24%) | 22 (25%) | .. |
| 365 days | 5·2 (6·3) | 5·5 (5·9) | 0·862 |

## Statistical Analysis

- Historically, survival to discharge (standard CPR): 6%
- Survival to discharge with good neurological outcome (MRS)=?
- For 6% in standard and 10.2 in intervention, sample size of 700 p'ts per group is needed.
  (0.049 significance with 80% statistical power)

## Statistical Analysis

- Fisher's exact test for analysis of primary endpoint
- p<0.05 = significant
- All analyses with StatXact version 8 and SPSS version 18.0

## For primary endpoint

- For the primary endpoint, treatment with study intervention led to a 53% relative increase in survival to hospital discharge with a modified Rankin scale score of 3 or less compared with standard CPR (odds ratio 1.58, 95% CI 1.07–2.36, p=0.019; table 2).
- Survival (to discharge) do not differ b/t ventricular fibrillation & pulseless ventricular tachycardia in both control and intervention (first recorded rhythm)

## Results

- Functional assessment :
  Disabilities rating scale scores did not differ b/t groups. 投影片 17
- Overall major adverse event rates did not differ. Major Adverse Events
- Consistent survival differences b/t groups were noted throughout study, independent of age, site, sex and date of treatment 投影片 29

## Major Adverse Events

- *

| | Standard CPR group (n=813) | Intervention* group (n=840) | p value |
|---|---|---|---|
| Patients with reported adverse events† | | | 0·681 |
| ≥1 | 766 (94%) | 787 (94%) | |
| 0 | 47 (6%) | 53 (6%) | |
| Adverse events | | | |
| Death | 729 (90%) | 734 (87%) | 0·165 |
| Rearrest | 161 (20%) | 184 (22%) | 0·304 |
| Pulmonary oedema‡ | 62 (8%) | 94 (11%) | 0·015 |
| Seizure after index arrest | 13 (2%) | 11 (1%) | 0·683 |
| Bleeding requiring transfusion or surgery | 3 (<1%) | 7 (<1%) | 0·343 |
| Chest fractures | 15 (2%) | 12 (1%) | 0·563 |
| Pneumothorax | 7 (<1%) | 10 (1%) | 0·628 |
| Haemothorax | 1 (<1%) | 2 (<1%) | 1·000 |
| Cardiac tamponade | 3 (<1%) | 2 (<1%) | 0·682 |
| Cerebral bleeding | 3 (<1%) | 2 (<1%) | 0·682 |
| Aspiration | 7 (<1%) | 8 (1%) | 1·000 |
| Internal organ injury | 2 (<1%) | 4 (<1%) | 0·687 |
| Other | 3 (<1%) | 1 (<1%) | 0·367 |
| Study device functionality | | | |
| Impedance-threshold device | | | |
| Timing light failure | NA | 59 (7%)§ | – |
| ACD-CPR device | | | |
| Inadequate attachment of suction cup to the chest | NA | 81 (9%)¶ | – |

## Results

- Therapeutic benefit of CPR (both grps) highly dependent on time to start of CPR.
- No survivors with favorable neurological function in either groups when CPR started >10mins after emergency call.

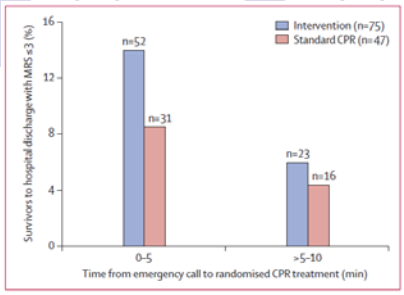



**Figure 6:** Survival at hospital discharge with favourable neurological function (MRS score ≤3 at discharge from hospital) by time to CPR treatment
Survival at hospital discharge with MRS ≤3 was significantly higher in the intervention group than in the standard CPR group (odds ratio 1·58, 95% CI 1·07–2·36, p=0·019). There were no survivors with favourable neurological function in either group if CPR was initiated more than 10 min after the emergency call. MRS=modified Rankin scale. CPR=cardiopulmonary resuscitation.

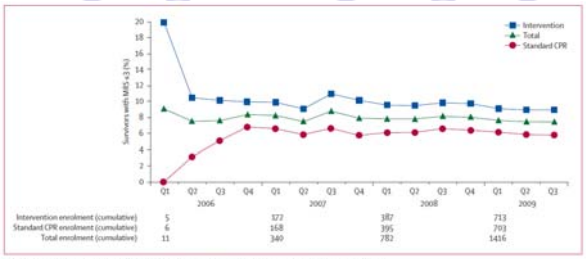



**Figure 5:** Cumulative rates of achievement of primary endpoint (MRS score ≤3 at discharge from hospital)
Results are shown for pivotal-phase enrolment (n=1652) by year quarter (Q). Consistent results in both groups were shown throughout the whole study. Enrolment was initiated in the fourth quarter of 2007 in Site 6 and the first quarter of 2009 in Site 7. MRS=modified Rankin scale. CPR=cardiopulmonary resuscitation.

## Age of p't surviving to discharge with MRS≦3

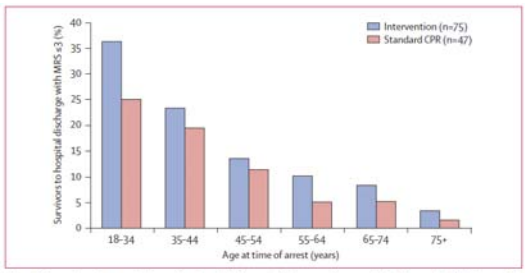



**Figure 3:** Age of patients surviving to hospital discharge with favourable neurological function (MRS score ≤3)
CPR=cardiopulmonary resuscitation. MRS=modified Rankin scale.[18]

## Results*

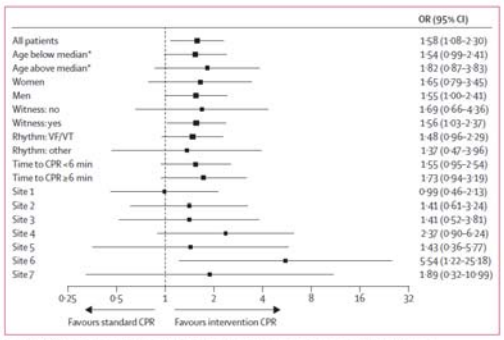



**Figure 4:** Effects of age, study site, sex, and treatment intervention on primary study endpoint
Estimated odds ratios exceeded 1·00 for subgroups based on age, sex, witnessed status, time to start of CPR, and all study sites apart from Site 1. VF/VT=ventricular fibrillation and pulseless ventricular tachycardia. CPR=cardiopulmonary resuscitation. *Median age was 67 years (IQR 56–79).

## Discussion

- ACD-CPR + ITD **significantly increases survival** to hospital discharge with favourable neurological function.
- Overall survival increased by nearly **50% by 1 year** in the intervention group.

- Consistency of benefit was independent of sex, age, date of enrolment, and study site.
- Neurological function was much **the same** between groups at 90 days and 365 days after the out-ofhospital cardiac arrest.

- Overall major adverse event rates: **no differences.**
- Occurrence of pulmonary edema was increased by 50% in the device group, which was coexistent with the increase in survival with favourable neurological function.
- return of spontaneous circulation and hospital admission rates: **no differences**.

- We suggest **greater blood flow improved cerebral perfusion** in the intervention group resulted in **reduced cerebral ischemia**.
- Improved perfusion outside the hospital in the intervention group could result in **more stable candidates for cardiac catheterisation** than were found in the standard CPR group

## Limitations

- Emergency medical service rescuers were not blinded.
- we could not establish the relative contribution of ACD-CPR alone, the ITD alone.

## Conclusion

- Thus, compared with standard CPR, ACD-CPR with ITD results in **significantly increased survival to hospital discharge with favourable neurological function**, which was observed to 1 year after out-of-hospital cardiac arrest.

Thanks for attention