# Survival for Nonshockable Cardiac Arrests Treated With Noninvasive Circulatory Adjuncts and Head/Thorax Elevation*



**OBJECTIVES:** Cardiac arrests remain a leading cause of death worldwide. Most patients have nonshockable electrocardiographic presentations (asystole/pulseless electrical activity). Despite well-performed basic and advanced cardiopulmonary resuscitation (CPR) interventions, patients with these presentations have always faced unlikely chances of survival. The primary objective was to determine if, in addition to conventional CPR (C-CPR), expeditious application of noninvasive circulation-enhancing adjuncts, and then gradual elevation of head and thorax, would be associated with higher likelihoods of survival following out-of-hospital cardiac arrest (OHCA) with nonshockable presentations.

**DESIGN:** Using a prospective observational study design (ClinicalTrials.gov NCT05588024), patient data from the national registry of emergency medical services (EMS) agencies deploying the CPR-enhancing adjuncts and automated head/thorax-up positioning (AHUP-CPR) were compared with counterpart reference control patient data derived from the two National Institutes of Health clinical trials that closely monitored quality CPR performance. Beyond unadjusted comparisons, propensity score matching and matching of time to EMS-initiated CPR ($T_{CPR}$) were used to assemble cohorts with corresponding best-fit distributions of the well-established characteristics associated with OHCA outcomes.

**SETTING:** North American 9-1-1 EMS agencies.

**PATIENTS:** Adult nontraumatic OHCA patients receiving 9-1-1 responses.

**INTERVENTIONS:** In addition to C-CPR, study patients received the CPR adjuncts and AHUP (all U.S. Food and Drug Administration-cleared).

**MEASUREMENTS AND MAIN RESULTS:** The median $T_{CPR}$ for both AHUP-CPR and C-CPR groups was 8 minutes. Median time to AHUP initiation was 11 minutes. Combining all patients irrespective of lengthier response intervals, the collective unadjusted likelihood of AHUP-CPR group survival to hospital discharge was 7.4% (28/380) vs. 3.1% (58/1,852) for C-CPR (odds ratio [OR], 2.46 [95% CI, 1.55–3.92]) and, after propensity score matching, 7.6% (27/353) vs. 2.8% (10/353) (OR, 2.84 [95% CI, 1.35–5.96]). Faster AHUP-CPR application markedly amplified odds of survival and neurologically favorable survival.

**CONCLUSIONS:** These findings indicate that, compared with C-CPR, there are strong associations between rapid AHUP-CPR treatment and greater likelihood of patient survival, as well as survival with good neurological function, in cases of nonshockable OHCA.

**KEYWORDS:** asystole; cardiopulmonary resuscitation; head-up/thorax-up cardiopulmonary resuscitation; nonshockable cardiac arrest; pulseless electrical activity

**Kerry M. Bachista, MD, FACEP, FAEMS**[1,2]

**Johanna C. Moore, MD, MSc, FACEP**[3]

**José Labarère, MD, PhD**[4]

**Remle P. Crowe, PhD**[5]

**Lauren D. Emanuelson, RN, BS, EMT-P**[6]

**Charles J. Lick, MD**[7]

**Guillaume P. Debaty, MD, PhD**[8]

**Joseph E. Holley, MD, FACEP, FAEMS**[9,10]

**Ryan P. Quinn, BS, EMT-P**[11]

**Kenneth A. Scheppke, MD, FAEMS**[12,13]

**Paul E. Pepe, MD, MPH, FAEMS, MCCM, MACP, FACEP, FRCP**[13–16]

***See also p. 331.**



**DOI: 10.1097/CCM.0000000000006055**

In North America and Europe alone, nearly 1 million persons experience nontraumatic sudden out-of-hospital cardiac arrest (OHCA) annually (1, 2). Most (75–85%) have "nonshockable" (NS) electrocardiographic

## KEY POINTS

**Question:** In addition to closely monitored conventional cardiopulmonary resuscitation (C-CPR), would application of circulatory-enhancing and intracranial pressure–lowering adjuncts improve survival after cardiac arrest with nonshockable (asystole/pulseless electrical activity) presentations?

**Findings:** Rapid treatment with the combination of several well-studied CPR adjuncts that increase circulation and gradually elevate the head and thorax was associated with a 2.5- to threefold overall significant improvement in survival-to-hospital discharge vs. C-CPR. Faster application significantly amplified the odds of surviving.

**Meaning:** The results predict the potential for restoring functional lives annually for tens of thousands of nonshockable cardiac arrest patients formerly considered to be largely unsalvageable.



presentations (1–10), either asystole or pulseless electrical activity (PEA).

Despite rapidly responding 9-1-1 emergency medical services (EMS), immediate delivery of basic cardiopulmonary resuscitation (CPR) and other longstanding, intensely researched treatments (oxygenation interventions, epinephrine infusions), nearly all OHCA patients fail to survive (SURV) to hospital discharge (1–12). The small minority of OHCA patients with shockable presentations may be highly salvageable, but only under certain circumstances, including early, well-performed CPR and rapid defibrillation within minutes (3, 6, 13, 14). Nonetheless, collectively in 2021, OHCA SURV chances in the United States, including shockable cases, still averaged less than or equal to 10% among progressive EMS systems that track outcomes and neurologically intact SURV was less than 6.5% (1, 3, 5–10).

Although the clear majority of NS-OHCA are unwitnessed events and often have lengthier response intervals, poor outcomes after NS-OHCA are also due to physiologic limitations of traditional CPR. Even for shockable cases, conventional CPR (C-CPR), performed early and appropriately, only provides ~20% of normal cerebral perfusion pressure (15–21). Chest compressions produce forward-flowing (arterial) pressure waves, but they also generate substantial retrograde venous pressure waves resulting in pulsatile increases in intracranial pressure with each compression, thus impairing trans-cerebral arterial flow (15–21). Coupled with limited refilling of cardiac chambers, C-CPR becomes progressively ineffective over time, especially with prolonged untreated cardiac arrest intervals (15, 16).

Recent laboratory and clinical investigations have demonstrated new mechanisms to mitigate some of these inherent limitations of C-CPR. Noninvasive adjuncts, including the impedance threshold device (ITD) or use of suction cup–based active-compression-decompression (ACD), have improved intrathoracic pressure regulation during CPR, both individually and particularly in combination (17–28). Leveraging these different, yet complementary, mechanisms of action, ITD/ACD-CPR lowers intracranial pressure, augments cardiac preload, and improves coronary and cerebral perfusion pressures (15, 17, 19). Multiple clinical trials of ITD/ACD-CPR have not only demonstrated improved hemodynamics and resuscitation rates but also a 50% improvement in 1-year survival with favorable neurologic function compared with C-CPR (24–28).

More recently, a comprehensive series of porcine ventricular fibrillation models identified a well-defined sequencing of interventions in which C-CPR is followed rapidly by ITD/ACD-CPR for 2 minutes, and then gradual head and thorax elevation over another 2 minutes. This well-studied cadence consistently results in near-normalization of cerebral perfusion pressures and profound improvements in neurologically favorable survival (17, 19, 20, 29–33). The pivotal adjuncts used to generate these synergistic physiologic benefits, including an automated head/thorax-up positioning (AHUP) device (**Fig. 1**), have all been cleared by the U.S. Food and Drug Administration and are now being introduced into clinical settings (22, 34, 35). Following institutional review board (IRB) approvals for collecting and publishing deidentified outcome data, a nationwide registry was established to track OHCA patients treated with this "neuroprotective" strategy prospectively (22, 35).

Early-adopting EMS agencies using first-in responders to provide the "AHUP-CPR" protocol already are reporting markedly increased likelihoods of patient SURV overall when evaluating both shockable and NS cases combined (22, 36). However, it had yet to be delineated if this CPR-enhancing approach is also

**Figure 1.** Illustration depicting the main complementary components of the triad of intracranial and intrathoracic pressure–lowering devices, including 1) impedance threshold device (ITD) attached to the airway; 2) a mechanical active-compression/decompression cardiopulmonary resuscitation (ACD-CPR) device encircling the chest with attached suction cup positioned at the manikin's sternum; and 3) depicted below the manikin, in a fully elevated position, an automated head/thorax-up positioning device that gradually elevates the head and thorax over 2 min after 2-min circulation priming using ITD-ACD augmentation of basic conventional CPR. A hand-held ACD-CPR pump for manual compression-decompression use is also shown (*bottom right corner*).

specifically effective for NS-OHCA and applicable subgroups. Therefore, the primary study objective was to compare SURV among NS-OHCA patients receiving the AHUP-CPR adjuncts vs. C-CPR controls managed in high-performance EMS systems. The main hypothesis was that, compared with C-CPR alone, the additional rapid application of AHUP-CPR was associated with improved SURV for NS-OHCA patients.

## MATERIALS AND METHODS

### IRB Approval and Clinical Trial Registration

The International Device-Assisted Controlled Sequential Elevation CPR Registry continues to receive de-identified patient data from EMS systems using all AHUP-CPR components: 1) suction cup-based ACD-CPR (ResQPUMP; ZOLL Medical, Chelmsford, MA) and/or automated-ACD (LUCAS; Stryker Medical, Kalamazoo, MI); 2) ITD (ResQPOD; ZOLL Medical); and 3) automated head/thorax elevation (EleGARD Patient Positioning System; AdvancedCPR Solutions, Edina, MN). The registry is a collaborative extension of intrinsic quality assurance processes routinely conducted by most governmental public safety agencies (3). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and that of the 1975 Helsinki Declaration. The registry, listed in ClinicalTrials.gov (identifier NCT05588024), received approval (HSR-17–4414) from the central WCG IRB (study 1281307) with "waiver of informed consent" (latest reapproval February 23, 2023).

### Participants

AHUP-CPR registry patients with nontraumatic NS-OHCA presentations were compared with counterpart C-CPR patients from two large-scale randomized clinical trials as reference controls (24, 37, 38). Study inclusion criteria for the AHUP-CPR patients were as follows: 1) aged 18 years or older; 2) AHUP-CPR treatment; 3) nontraumatic NS-presentation; and 4) treatment in agencies using first-in responders for AHUP-CPR and prospectively/consistently recording: 1) elapsed-time from 9-1-1 call receipt to EMS initiating basic C-CPR ($T_{CPR}$); 2) 9-1-1 call to AHUP device placement/activation ($T_{AHUP}$); 3) all outcome-related data including age, sex, bystander-witnessed event, EMS-witnessed, bystander-performed CPR, electrocardiographic presentation, and outcomes, including SURV and neurologically favorable survival. The five early-adopting EMS agencies voluntarily participating in the AHUP-CPR registry and meeting these enrollment criteria were from: Peoria, IL; St. Johns County, FL; Anoka, MN; Edina, MN; Germantown, TN; all geographically, demographically, and operationally diverse (22, 35, 36). Although these AHUP agencies had variable start dates (earliest, April 2019; latest March 2021), most patients were entered during 2020–2021. By prospective design, enrollment for this analysis ended December 31, 2021.

The C-CPR data were obtained specifically from the Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation using an IMpedance valve and Early versus Delayed analysis (PRIMED) trial and the Impact of an ITD and Active Compression Decompression CPR on Survival From Out-of-Hospital Cardiac Arrest (ResQ) control arms because these trials involved greater than 150 U.S. and Canadian EMS agencies ranging in size, demographics, and geographical location (24, 37, 38). Funded and closely monitored by the National Institutes of Health (NIH), both stipulated prospective collection of the same study variables and outcome-related data tracked for AHUP-CPR. Furthermore, these independent trials were targeted to establish the most stringent comparisons because both involved recognized high-performing EMS agencies, including those that the NIH required recorded documentation of quality CPR performance system wide prior to permitting agency participation/enrollment, as well as ongoing documentation throughout the trial (37, 38). NS-OHCA control group outcomes from each trial were similar and each matched, or surpassed, current data from progressive U.S. EMS systems monitoring outcomes with standardized metrics (1, 3).

## Study Design and Protocol

The prospective observational population-based study design entailed a noncontemporaneous, nonrandomized clinical trial with both direct (unadjusted) head-to-head evaluations and propensity score–matched comparisons of NS-OHCA patient SURV using C-CPR vs. C-CPR plus AHUP-CPR. Propensity score analyses incorporated all well-established OHCA outcome-related variables (5, 9, 10, 36, 39–41).

Personnel at every site were trained in C-CPR and advanced life support according to the American Heart Association guidelines (11, 22, 35, 37, 38). AHUP-CPR personnel received additional training in AHUP-CPR techniques prior to agency implementation. Clinical care protocols included immediate C-CPR initiation, early automated external defibrillator application, and rapid AHUP device placement while initiating ventilation (via facemask, endotracheal tube, and/or supraglottic airway) combined with ITD application and transitioning of C-CPR to manual ACD-CPR and/or mechanical ACD-CPR. Periodic retraining focused on minimizing chest compression interruptions mandating less than 6-second pauses for mechanical-CPR or AHUP applications.

Placement in an AHUP device immediately elevates the head/thorax to 12 cm (occiput) and 8 cm (mid-thorax/heart), respectively. Following a 2-minute interval for circulatory priming with ITD/ACD-CPR, the activated AHUP device gradually elevates the head/thorax over 2 minutes, to 24/12 cm, respectively (19, 30, 31). Mechanical ACD-CPR devices attach directly to AHUP device backplates, stabilizing mid-sternal positioning, and reducing device drift/movement during compressions (Fig. 1). After the return of spontaneous circulation, compressions were halted and the ITD was removed, but patients generally remained in the AHUP device with the head/thorax elevated as long as their systolic arterial pressure remained greater than 90 mm Hg. The ITD and ACD-CPR interventions were resumed if the patient had a recurrent cardiac arrest.

## Study Endpoints

The primary endpoint was SURV. Secondary outcomes included return of spontaneous circulation and SURV with favorable neurologic function defined as Cerebral Performance Category score of 1–2 or modified Rankin Score less than or equal to 3 (1, 3, 24, 37, 39).

## Statistical Analysis

Summary descriptive statistics for pertinent patient characteristics were reported as numbers and percentages for categorical variables, and means with SDs, or medians along with 25th and 75th percentiles (interquartile range [IQR]), wherever appropriate, for continuous variables. Unadjusted primary and secondary outcomes were compared between AHUP-CPR and C-CPR cohorts using crude odds ratios (OR) and 95% CIs. Exploratory subgroup analyses also were performed to further document the impact of $T_{AHUP}$ on outcomes as well as PEA, asystole, witnessed, and unwitnessed arrest subcategories.

To account for potential confounding effects by imbalances in baseline characteristics, propensity score matching and $T_{CPR}$ matching also were performed (40, 41). Propensity scores were derived initially from a nonparsimonious multivariable logistic regression model predicting receipt of AHUP-CPR with relevant outcome-related covariates: age, sex, EMS-witnessed arrest, bystander-witnessed arrest, and bystander CPR (5, 40, 41). C-CPR patients with the nearest propensity score caliper of 0.01 and the same discrete $T_{CPR}$ interval were then matched one-to-one, without replacement, to each AHUP-CPR recipient. With this approach, C-CPR patients would not be matched inadvertently with AHUP-CPR recipients already achieving return of spontaneous circulation (42).

Success of propensity score and $T_{CPR}$ matching was evaluated further by checking for adequate overlap in propensity scores between study groups and computing standardized differences for baseline characteristics. A standardized difference of greater than or equal to 10% after matching was considered, a priori, to be indicative of residual imbalance in baseline characteristics (40, 41).

Both OR and 95% CI were calculated using logistic regression after propensity score and $T_{CPR}$ matching. Based on prior study findings, ORs were examined in a prespecified comparative analysis of clinical outcomes stratified by 1-minute increases in $T_{AHUP}$ (22, 35). Two-sided $p$ values of less than 0.05 were considered statistically significant. Statistical analyses used Stata/SE, Version 16.0 (StataCorp, College Station, TX).

## RESULTS

### Baseline Characteristics of Patients

From registry inception until closing enrollment for this analysis (December 31, 2021), 965 OHCA patients from 11 EMS systems received AHUP-CPR without any observed safety/complication issues. The five EMS agencies meeting inclusion criteria (first-in responders using AHUP-CPR/comprehensive datasets) provided 467 OHCA patients receiving AHUP-CPR among whom 380 (81%) had NS-OHCA presentations (**Fig. 2**). Among those 380 receiving AHUP-CPR and 1,852 receiving C-CPR, asystole or PEA was well documented (electrocardiographic record) in 342 of 380 (90%) and 1,722 of 1,852 (93%), respectively. The remaining were reported only as "nonshockable".

Patient characteristics were similar overall between study agencies and other registry sites (**Supplementary Table S1**, http://links.lww.com/CCM/H425). Among 494 total patients initially encountered with NS arrests across the five agencies enrolling patients, AHUP-CPR was not applied to 114 patients for reasons described in **Supplementary Tables S2** and **S3** (http://links.lww.com/CCM/H425) such as those experiencing OHCA after/during ambulance transport or those regaining pulses prior to AHUP application.

Two-thirds ($n$ = 252/380) received a sequential application of ACD devices, starting with the manual ACD and later transitioning to automated ACD, while 13% ($n$ = 50) received manual ACD only and 20% ($n$ = 78) received only automated ACD. Half the time, there were only two or three responders initially on-scene applying AHUP-CPR.

Although comparative percentages of asystole presentations were well-aligned before propensity score matching (61% [230/380] AHUP-CPR vs. 62% C-CPR

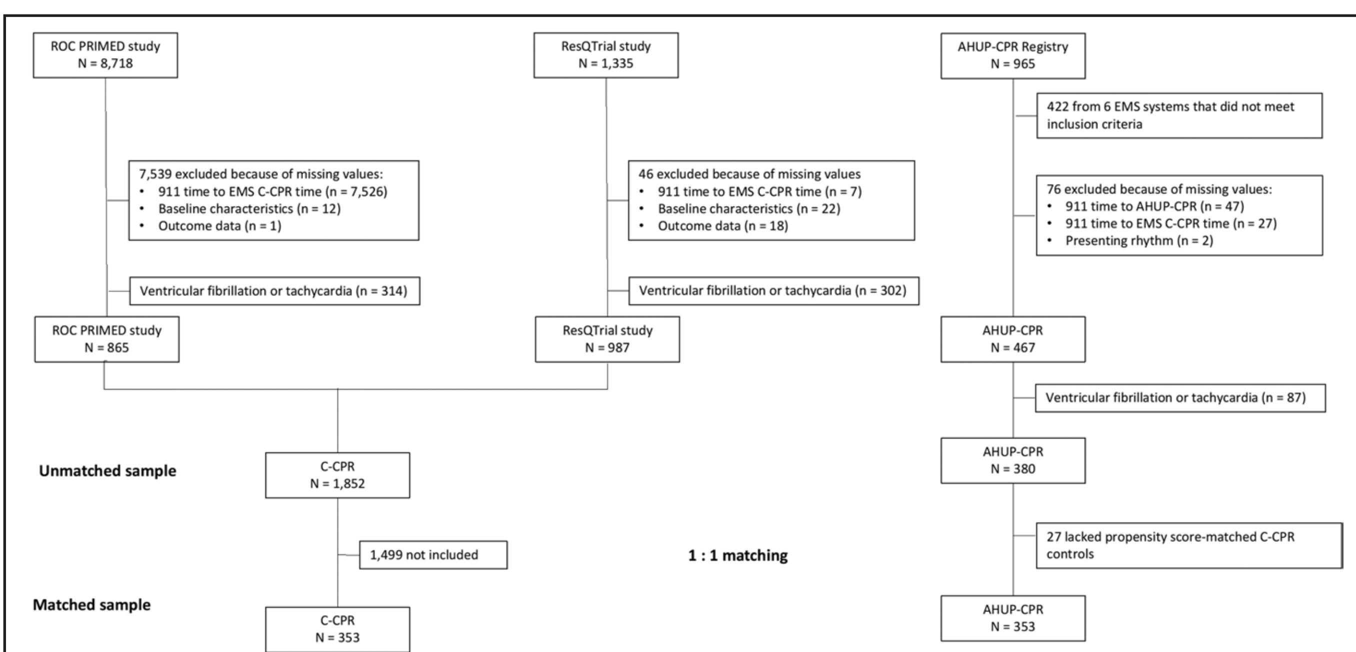


**Figure 2.** Study enrollment flowchart. Flowchart tracking the process of how both control and study arm patients with nonshockable electrocardiographic presentations were selected and enrolled into the current study. AHUP = automated head/thorax-up positioning, C-CPR = conventional cardiopulmonary resuscitation, EMS = emergency medical services, ROC PRIMED = Resuscitation Outcomes Consortium Prehospital Resuscitation using an IMpedance valve and Early versus Delayed analysis trial (37), ResQTrial = the Active Compression Decompression CPR on Survival From Out-of-Hospital Cardiac Arrest trial (24).

[1,144/1,852]), asystolic AHUP-CPR patients were, more frequently, unwitnessed arrests; 73% (168/230) vs. 67% (766/1,144) of asystolic C-CPR patients ($p = 0.07$). Before propensity-matching, AHUP-CPR patients had more bystander CPR attempts (47% vs. 33%; **Table 1**), but there was a much greater proportion of C-CPR patients with EMS-witnessed arrests (12% vs. 5% AHUP cases).

## Unadjusted Analyses

In unadjusted analyses, return of spontaneous circulation rates for AHUP-CPR (33% [125/380]) and C-CPR (29% [535/1,852]) patients were not statistically different (OR, 1.21 [95% CI, 0.95–1.53]). In contrast, likelihood of SURV (**Fig. 3**) and SURV with favorable neurologic function (**Table 2**) were 2.5- to three-fold higher with AHUP-CPR. Comparing all cases irrespective of response intervals, SURV, the primary study endpoint, was 7.4% (28/380) vs. 3.1% (58/1,852) for C-CPR (OR, 2.46 [95% CI, 1.55–3.92]).

In subgroup analyses of PEA presentations, AHUP-CPR was associated with higher odds of SURV (13.4% [15/112] vs. 6.2% [36/578]; OR, 2.33 [95% CI, 1.23–4.41]) and SURV with favorable neurologic function (9.8% [11/112] vs. 2.8% [16/578]; OR, 3.83 [95% CI, 1.73–8.48]).

Among all asystole patients (witnessed and unwitnessed), including those with lengthier $T_{CPR}$, AHUP-CPR had overall higher odds of SURV (4.8% [11/230] vs 1.7% [20/1,144]; OR, 2.82 [95% CI, 1.33–5.97]), but significance was not reached statistically for SURV with favorable neurologic function (1.3% [3/230] vs. 0.8% [9/1,144]; OR, 1.67 [95% CI, 0.45–6.20]). However, when specifically examining unwitnessed/asystole arrests (44% and 41%, respectively, of all NS-OHCA cases), AHUP-CPR was associated with a much higher likelihood of both SURV (4.2% [7/168] vs. 0.7% [5/766]; OR, 6.62 [95% CI, 2.07–21.11]) and SURV with favorable neurologic function (1.8% [3/168] vs. 0.3% [2/766]; OR, 6.95 [95% CI, 1.15–41.90]).

## TABLE 1.
**Unadjusted Direct Comparisons of Nontraumatic Cardiac Arrest Patients With Nonshockable Presentations Who Received Conventional Cardiopulmonary Resuscitation Versus Those Who Additionally Received Circulation-Enhancing Adjuncts and Automated Head/Thorax-Up Positioning**

| Characteristics | Conventional CPR | AHUP-CPR | Standardized Difference (%) |
|---|---|---|---|
| Total no. of patients | 1,852 | 380 | |
| Mean age, yr (±SD) | 67.0 (±16.8) | 65.7 (±16.6) | 7.6 |
| Male sex, *n* (% of cases) | 1,130 (61) | 256 (67) | −13.3 |
| EMS witnessed, *n* (%) | 215 (12) | 19 (5.0) | 24.1 |
| Bystander witnessed, *n* (%) | 636 (34) | 126 (33) | 2.5 |
| Bystander CPR attempt, *n*. (%) | 612 (33) | 180 (47) | −29.5 |
| Median time (min) from 9-1-1 call to EMS initiating basic CPR (IQR) | 8 (6–10) | 8 (6–11) | −0.9 |
| Median time (min) from 9-1-1 call to AHUP activation (IQR | – | 11 min (9–15 min) | – |
| Contributing studies, *n* (%) | | | |
| AHUP Registry | – | 380 (100) | |
| Resuscitation Outcomes Consortium-PRIMED | 865 (47%) | – | |
| ResQTrial | 987 (53%) | – | |
| Unadjusted mean propensity score (±SD) | 0.17 (±0.05) | 0.19 (±0.05) | −37.0 |

AHUP-CPR = conventional cardiopulmonary resuscitation with the addition of circulatory adjuncts and automated head-up positioning, CPR = cardiopulmonary resuscitation, EMS = emergency medical services, IQR = interquartile range (25th–75th percentiles).
Resuscitation Outcomes Consortium-PRIMED is one of the two National Institutes of Health (NIH) clinical trials used to derive a conventional-CPR control population and ResQTrial is the other NIH trial.

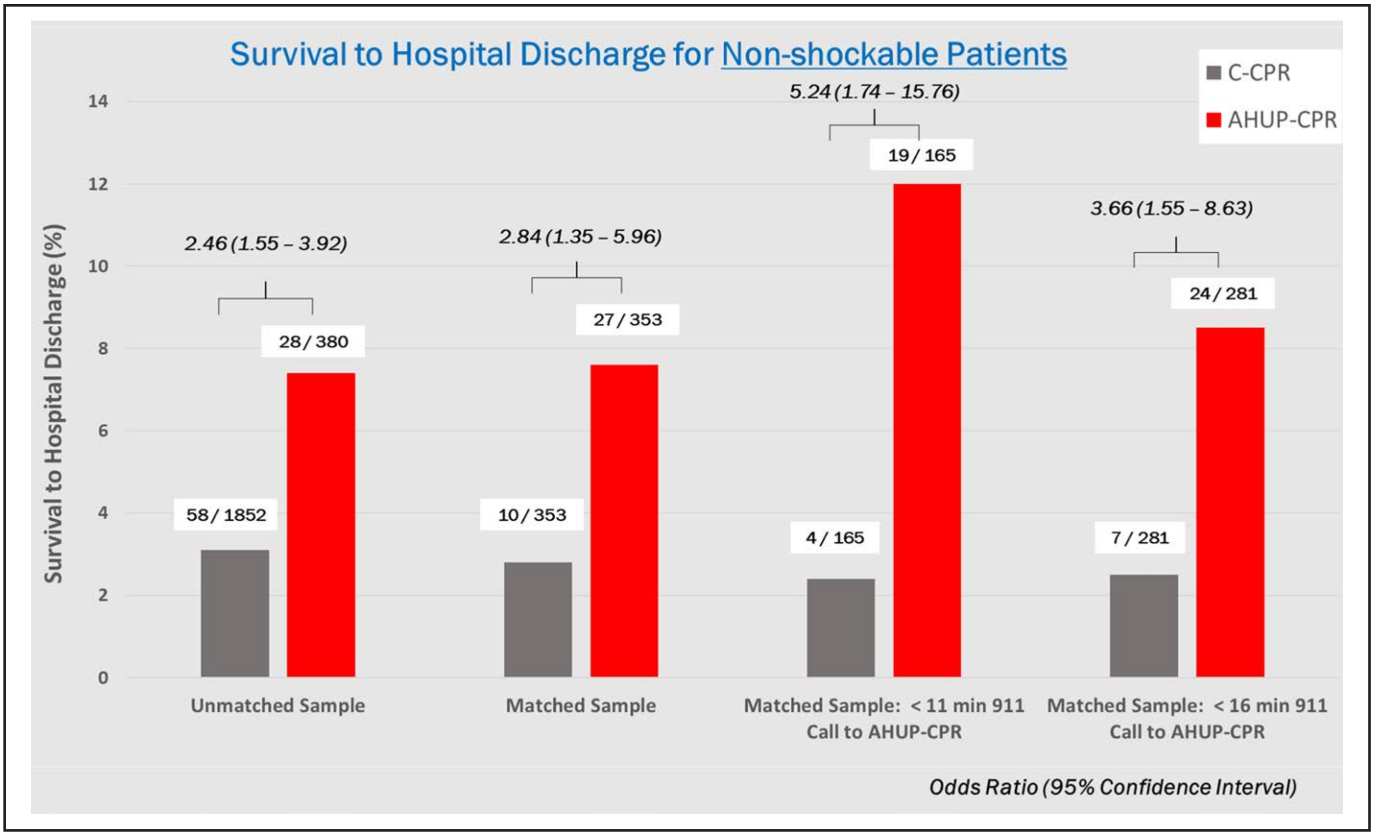


**Figure 3.** Proportions of cardiac arrest patients surviving to hospital discharge (SURV) after nonshockable electrocardiographic presentations (asystole/pulseless electrical activity), comparing a large cohort receiving conventional cardiopulmonary resuscitation (C-CPR) (*gray columns*) to patients additionally receiving the triad of noninvasive intracranial/intrathoracic pressure–lowering devices, including an automated head/thorax-up positioning (AHUP) device (*red columns*). The first *gray/red column*s represent head-to-head (unmatched) comparison of all cases, including those with extended response intervals (20% of cases); second comparison represents propensity score/$T_{CPR}$-matched analyses ($T_{CPR}$ = time elapsed from 9-1-1 call receipt until basic CPR initiation by emergency medical services). The last two *gray/red columns* involve matched samples that are compared according to time until AHUP application ($T_{AHUP}$) using the median $T_{AHUP}$ (<11 min) and $T_{AHUP}$ 80th percentile (<16 min) as examples. Odds ratios and 95% CIs are also indicated.

## Propensity Score– and Time Interval–Matched Analyses

Based on propensity score and discrete $T_{CPR}$ intervals, 353 AHUP-CPR patients (93%) could be fully matched with 353 C-CPR patients (Fig. 2). Adequate overlap in propensity scoring was observed between study groups and matching was successful in attenuating imbalances in baseline characteristics with standardized differences less than 10% for all variables (**Table 3**).

Even after propensity score and $T_{CPR}$ matching, comparable, relatively high rates of return of spontaneous circulation were still observed in both groups: AHUP-CPR (33% [118/353]) and C-CPR (29% [101/353]; OR, 1.25 [95% CI, 0.91–1.72]). In contrast (Fig. 3 and Table 2), AHUP-CPR was associated with higher probabilities of SURV (7.6% [27/353] vs. 2.8% [10/353]; OR, 2.84 [95% CI, 1.35–5.96]) and SURV with favorable neurologic function (4.2% [15/353] vs. 1.1% [4/353]; OR, 3.87 [95% CI, 1.27–11.78]).

## Time Dependency of Outcomes

The median $T_{CPR}$, before and after propensity score matching, was 8 minutes (IQR = 6–10) for both AHUP-CPR and C-CPR (Tables 1 and 3). Median $T_{AHUP}$ remained 11 minutes (IQR = 9–15), before and after matching (Tables 1 and 3). The sooner AHUP-CPR was initiated, the better the outcome. For example, when $T_{AHUP}$ less than 11 minutes (median $T_{AHUP}$ before and after matching), SURV estimates for AHUP-CPR relative to C-CPR (Fig. 3) were 11.5% (19/165) vs. 2.4% (4/165; OR, 5.24 [95% CI, 1.74–15.76]). For $T_{AHUP}$ less than 16 minutes (i.e., 80th percentile of all matched AHUP-CPR cases), SURV was 8.5% (24/281) vs. 2.5% (7/281; OR, 3.66 [95% CI, 1.55–8.63]). $T_{CPR}$-related

## TABLE 2.

### Number of Patients Surviving With Favorable Neurologic Function After Nonshockable Cardiac Arrest Presentations, Comparing Those Receiving Conventional Cardiopulmonary Resuscitation Techniques to Those Also Receiving Circulation-Enhancing Adjuncts and Automated Head/Thorax-Up Positioning

| | Conventional CPR | AHUP-CPR | |
|---|---|---|---|
| | n (%) | *n (%)* | Odds Ratio (95% CI) |
| Unmatched (unadjusted) analysis of no. surviving (%) | 26/1,852 (1.4) | 16/380 (4.2) | 3.09 (1.64–5.81) |
| Propensity score–matched analysis using all cases including those with lengthier response intervals, *n* surviving (%) | 4/353 (1.1%) | 15/353 (4.2%) | 3.87 (1.27–11.78) |
| Time from 9-1-1 call receipt to AHUP-CPR activation using median and 80th percentile of response intervals, *n* surviving (%) | | | |
| <11 min (47% of all cases) | 1/165 (0.6) | 10/165 (6.1) | 10.58 (1.34–83.63) |
| <16 min (80% of all cases) | 1/281 (0.4) | 13/281 (4.6) | 13.58 (1.76–104.54) |

AHUP-CPR = conventional cardiopulmonary resuscitation with addition of circulatory adjuncts and automated head/thorax-up positioning, CPR = cardiopulmonary resuscitation, no. = number of survivors.

## TABLE 3.

### Characteristics of Cardiac Arrest Patients With Nonshockable Presentations After Propensity Score Matching, Comparing Those Recei)ving Conventional Cardiopulmonary Resuscitation to Those Also Adding Circulation-Enhancing Adjuncts and Automated Head/Thorax-Up Positioning

| Characteristics | Conventional CPR | AHUP-CPR | Standardized Difference (%) |
|---|---|---|---|
| No. of patients | 353 | 353 | |
| Mean age, yr (±SD) | 66.5 (±16.0) | 65.9 (±16.3) | 3.7 |
| Male sex, *n*. (%) | 251 (71) | 236 (67) | 9.2 |
| EMS witnessed, *n* (%) | 17 (4.8) | 17 (4.8) | 0.0 |
| Bystander witnessed, *n* (%) | 106 (30) | 118 (33) | –7.3 |
| Bystander CPR attempt, *n* (%) | 151 (43) | 166 (47) | –8.5 |
| Median time (min) from 9-1-1 call to EMS start of CPR (IQR) | 8 (6–10) | 8 (6–10) | 0.0 |
| Median time (min) from 9-1-1 call to AHUP activation (IQR) | – | 11 (9–15 | – |
| Contributing studies, *n* (%) | | | |
| AHUP Registry | | 353 (100) | |
| Resuscitation Outcomes Consortium-PRIMED | 178 (50) | | |
| ResQTrial | 175 (50) | | |
| Mean propensity score (±SD) | 0.18 (±0.05) | 0.18 (±0.05) | –1.7 |

AHUP-CPR = conventional cardiopulmonary resuscitation with the addition of circulatory adjuncts and automated head-up positioning, CPR = cardiopulmonary resuscitation, EMS = emergency medical services, IQR = interquartile range (25th–75th percentiles), PRIMED = Resuscitation Outcomes Consortium Prehospital Resuscitation using an IMpedance valve and Early versus Delayed analysis trial, ResQTrial = Impact of an ITD and Active Compression Decompression CPR on Survival From Out-of-Hospital Cardiac Arrest. Resuscitation Outcomes Consortium-PRIMED (37) is one of the two National Institutes of Health (NIH) clinical trials used to derive a conventional-CPR control population and the ResQTrial (24) is the other NIH trial.

differences were even more pronounced in SURV with favorable neurologic function (Table 2).

## DISCUSSION

This study provides strong evidence that, compared with traditional closed-chest manual CPR performed in the supine/horizontal plane, OHCA patients with NS presentations can now have far higher likelihoods of SURV when treated by first-in responders who can amplify the lifesaving effects of C-CPR with rapid deployment of AHUP-CPR. These results confirm recent investigational breakthroughs in understanding the pivotal, synergistic role that gradual head/thorax elevation can play when combined with ITD/ACD-CPR (15, 17–23, 30–33).

For over a half-century, until development of these new physiologically advantageous approaches, there was little new to offer NS-OHCA patients, even though they constitute the predominant majority of OHCA cases. The magnitude of the SURV benefit for NS patients in this study was pronounced, especially when AHUP-CPR was initiated within a quarter-hour of the 9-1-1 call for help, an achievable goal in nearly all U.S. EMS systems. Though survival percentages still remain relatively low among these severely anoxic patients, the magnitude of applicable case numbers is immense. As such, the results presented here, just for out-of-hospital NS cases, could translate into restoring functional lives for well over 10,000 patients/yr in the United States alone, and likely many more if even faster responses and "pit-crew" applications can be achieved routinely (1–3, 14, 36, 43).

Statistically, there were no significant differences in rates of return of spontaneous circulation which, compared with most OHCA databases, were relatively high (3). That observation could further attest to the quality of the high-performance EMS systems involved in the control arm. However, there were clear and statistically significant differences in SURV and especially SURV with good neurologic function for the typically futile resuscitation efforts experienced with unwitnessed/asystole presentations. These observations may therefore reflect the presumptive "neuroprotective" effects of this enhanced physiologic approach to resuscitation which has consistently generated normal (or near-normal) cerebral perfusion pressures and end-tidal $CO_2$, both in the laboratory and now in patients as well (19, 29–32, 44–46).

The results here may even underestimate the impact of AHUP-CPR for several reasons. For example, the primary outcome findings, as presented, probably were attenuated to some degree by inclusions of every NS case encountered, including outliers with very prolonged response delays. Also, to provide a more rigorous evaluation, AHUP-CPR outcomes were compared purposely to best-performing EMS systems, those recruited by the NIH for that reason. Not only was there NIH support and compliance monitoring, but all sites closely scrutinized CPR performance with electronic recordings, presumably optimizing C-CPR quality in the control arm (3, 24, 37, 38). Furthermore, most AHUP-CPR data were collected during the COVID-19 pandemic which created exponential increases in NS-OHCA cases worldwide, mostly asystolic/unwitnessed arrests with futile outcomes (47). Despite these many offsetting factors and disadvantages, AHUP-CPR still was associated with strikingly higher likelihoods of SURV for NS-OHCA patients, whether analyzed as a grouped cohort or stratified for PEA, asystole, witnessed/unwitnessed subgroups or time to treatment (5, 9).

One caveat usually expressed about adoption of any clinical intervention is that traditional randomized controlled trials should be conducted (48). However, recognizing that OHCA populations are extremely heterogeneous and that outcomes are affected by numerous complex factors, controlled clinical trials have been challenging, especially considering when unwitnessed OHCAs with NS presentations (36, 49, 50). Nonetheless, all of the known key outcome-related variables in OHCA have been well-studied and well-documented for decades (5, 7–10, 36). Accordingly, in this particular circumstance, the application of propensity score matching is a validated and statistically robust methodology, well-suited for such OHCA studies (5, 7–9, 40–42, 49, 50).

Furthermore, this current evaluation is a follow-up enhancement to the initial proof-of-concept investigation, a randomized controlled trial that confirmed neurologically favorable lifesaving using just the foundational ACD/ITD elements of AHUP-CPR (24). The addition, timing, and degree of head elevation components, meticulously and methodically fine-tuned in the laboratory over the past decade, clearly deliver a consistent and synergistic CPR-amplifier effect (17, 19, 20, 23, 29, 31, 32). These collective findings are further supported by indicators of restored circulation in patients such as normalization of end-tidal $CO_2$ ($Etco_2$) during CPR (45, 46).

Considering that AHUP-CPR and C-CPR study sites were somewhat different and enrollment noncontemporaneous, the design features could, theoretically, introduce unknown variables. However, this concern is less worrisome recognizing both current and longstanding NS-OHCA outcome experiences in all EMS systems worldwide, regardless of demographics, capabilities, and individual system track records (1–4, 7–10). Furthermore, most U.S. systems have equivalent types of rescuers and training, all using the same longstanding guidelines for NS-OHCA (3, 11). Irrespective of study design, additional training, and any other potential study effects at implementation (35, 48), both the unadjusted and adjusted AHUP-CPR SURV findings and their magnitude, are difficult to ignore, especially because nearly half the AHUP-CPR cases were unwitnessed/asystole and many had lengthy $T_{CPR}$. The raw data demonstrating 13% SURV for all PEA cases, and 4.2% SURV for all unwitnessed/asystole cases, are stand-alone major accomplishments (6–10).

Another important stipulation is that the AHUP-CPR strategy must be implemented rapidly with proper sequencing, timing, and tools (43, 51). Similar to automated external defibrillators, faster use improves survival, yet with a wider lifesaving window for both shockable and NS presentations (5, 13, 14, 22, 43, 51). Consequently, AHUP-CPR should be deployed with well-trained first-in responders such as firefighters, lifeguards, emergency department, ICU staff, and even trained security personnel (43, 51). Fittingly, the best results came from EMS crews who created specialized backpacks that both facilitated rapid carriage to the patient and opened up with each resuscitative tool strategically placed, a true pit-crew tactic further accelerating on-site interventions (22, 35, 36, 51). Emergency department and ICU teams may even have the advantages of having their cardiac arrest cases being witnessed and monitored.

Finally, EMS systems that adopt AHUP-CPR should also focus on other "chain of survival" essentials, from dispatcher-CPR instructions to post-resuscitation cardiac catheterization access and temperature management, as indicated (36). AHUP-CPR, though a significant breakthrough, is just one strategy to augment survival odds.

## CONCLUSIONS

Based on these analyses, OHCA patients with NS presentations, including those with unwitnessed arrest and asystole, will have a much higher likelihood of surviving with good neurologic function when chest compressions are augmented by expedient application of the noninvasive tools used in this study. In turn, rapid-responding EMS agencies, other first-in responders, and in-hospital staff should now be encouraged to adopt and further investigate this evolving neuroprotective CPR strategy.

## ACKNOWLEDGMENTS

We extend our gratitude to the many emergency medical services agencies and their respective emergency care responders who: 1) trained and participated in applying these progressive clinical care techniques rapidly and correctly; 2) ensured conscientious and accurate data collection; and 3) provided follow-up information that assured the integrity and quality of the evolving registry and its database.

1 *Department of Emergency Medicine, Mayo Clinic Alix School of Health Sciences, Mayo Clinic in Florida, Jacksonville, FL.*

2 *Emergency Medical Services Division, St. Johns County Fire Rescue, St. Augustine, FL.*

3 *Hennepin Healthcare, Department of Emergency Medicine, University of Minnesota School of Medicine, Minneapolis, MN.*

4 *Quality of Care Unit, Université Grenoble Alpes, Grenoble, France.*

5 *Clinical and Operational Research, ESO, Austin, TX.*

6 *Division of Quality Improvement and Compliance, Advanced Medical Transport of Central Illinois, Peoria, IL.*

7 *Division of Emergency Medical Services, Allina Health, Minneapolis, MN.*

8 *Department of Emergency Medicine, University Hospital of Grenoble Alpes, Grenoble, France.*

9 *Memphis Fire Department, City of Memphis, TN.*

10 *Division of Emergency Medical Services, State of Tennessee Department of Health, Nashville, TN.*

11 *EMS Division, City of Edina Fire Department, Edina, MN.*

12 *Florida Department of Health, Tallahassee, FL.*

13 *Office of the Medical Director, Palm Beach County Fire Rescue, West Palm Beach, FL.*

14 *Department of Management, Policy and Community Health, University of Texas Health Sciences Center, Houston, School of Public Health, Houston, TX.*

15 *Dallas County Fire Rescue Department, Dallas County, Dallas, TX.*

*16 Executive Offices, Metropolitan EMS Medical Directors Global Alliance, Fort Lauderdale, FL.*

*Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).*

*No extramural grants or funding were used at the various participating study sites to conduct this investigation of out-of-hospital cardiac arrest (OHCA) management. The cardiac arrest management training, data collection, and quality assurance functions are routine functions for emergency medical public safety agencies. AdvancedCPR Solutions, the manufacturer of one of the multiple devices used in this study, provided funding for the initial WCG IRB registration and also to the Hennepin Healthcare Research Institute for data management resources under the independent direction of Dr. Moore.*

*The authors have disclosed that they do not have any potential conflicts of interest.*

*For information regarding this article, E-mail: Dr.PaulPepe@GMail.com*

*ClinicalTrials.gov identifier: NCT05588024; https://clinicaltrials.gov/ct2/show/NCT05588024.*

*Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.*

*Work performed at multiple agencies in the United States. Data were managed and analyzed under the supervision of the Principal Investigator, Dr. Moore, at the Department of Emergency Medicine, University of Minnesota School of Medicine, and Hennepin Healthcare Research Institute.*



## REFERENCES


1. Tsao CW, Aday AW, Almarzooq ZI, et al: American Heart Association heart and stroke statistics—2022 update. *Circulation* 2022; 145:e153–e639
2. Sudden Cardiac Arrest Foundation Website. Available at: https://www.sca-aware.org/about-sudden-cardiac-arrest/latest-statistics#:~:text=According%20to%20the%20report%2C%20cardiac,nearly%201%2C000%20people%20each%20day. Accessed April 17, 2023
3. Cardiac Arrest Registry to Enhance Survival (C.A.R.E.S.) Website. Available at: https://mycares.net/sitepages/uploads/2022/2021_flipbook/index.html?page=34. Accessed April 17, 2023
4. Thomas AJ, Newgard CD, Fu R, et al: Survival in out-of-hospital cardiac arrests with initial asystole or pulseless electrical activity and subsequent shockable rhythms. *Resuscitation* 2013; 84:1261–1266
5. Sasson C, Rogers MAM, Dahl J, et al: Predictors of survival from out-of-hospital cardiac arrest – A systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010; 3:63–81
6. Pepe PE, Levine RL, Fromm RE, et al: Cardiac arrest presenting with rhythms other than ventricular fibrillation: Contribution of resuscitation efforts toward total survivorship. *Crit Care Med* 1993; 21:1838–1843
7. Andrew E, Nehme Z, Lijovic M, et al: Outcomes following out-of-hospital cardiac arrest with an initial cardiac rhythm of asystole or pulseless electrical activity in Victoria, Australia. *Resuscitation* 2014; 85:1633–1639
8. Herlitz J, Svensson L, Engdahl J, et al: Characteristics and outcome in out-of-hospital cardiac arrest when patients are found in a non-shockable rhythm. *Resuscitation* 2008; 76:31–36
9. Kuisma M, Jaara K: Unwitnessed out-of-hospital cardiac arrest: Is resuscitation worthwhile? *Ann Emerg Med* 1997; 30:69–75
10. Herlitz J, Engdahl J, Svensson L, et al: Can we define patients with no chance of survival after out-of-hospital cardiac arrest? *Heart* 2004; 90:1114–1118
11. Panchal AR, Bartos JA, Cabanas JG, et al; Adult Basic and Advanced Life Support Writing Group: Part 3: Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2020; 142:S366–S468
12. Perkins GD, Chen J, Deakin CD, et al: Randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2018; 379:711–721
13. Caffrey SL, Willoughby PJ, Pepe PE, et al: Public use of automated defibrillators. *N Engl J Med* 2002; 347:1242–1247
14. Song J, Guo W, Lu X, et al: The effect of bystander cardiopulmonary resuscitation on the survival of out-of-hospital cardiac arrests: A systematic review and meta-analysis. *Scand J Trauma Resusc Emerg Med* 2018; 26:86
15. Lurie KG, Nemergut EC, Yannopoulos D, et al: The physiology of cardiopulmonary resuscitation. *Anesth Analg* 2016; 122:767–783
16. Lee SK, Vaagenes P, Safar P, et al: Effect of cardiac arrest time on cortical cerebral blood flow during subsequent standard external cardiopulmonary resuscitation in rabbits. *Resuscitation* 1989; 17:105–117
17. Ryu HH, Moore JC, Yannopoulos D, et al: The effect of head-up cardiopulmonary resuscitation on cerebral and systemic hemodynamics. *Resuscitation* 2016; 102:29–34
18. Pirrallo RG, Aufderheide TP, Provo TA, et al: Effect of an inspiratory impedance threshold device on hemodynamics during conventional manual cardiopulmonary resuscitation. *Resuscitation* 2005; 66:13–20
19. Moore JC, Segal N, Lick MC, et al: Head and thorax elevation during active compression decompression cardiopulmonary resuscitation with an impedance threshold device improves cerebral perfusion in a swine model of prolonged cardiac arrest. *Resuscitation* 2017; 121:195–200
20. Moore JC, Salverda B, Rojas-Salvador C, et al: Controlled sequential elevation of the head and thorax combined with active compression decompression cardiopulmonary resuscitation and an impedance threshold device improves neurological survival in a porcine model of cardiac arrest. *Resuscitation* 2021; 158:220–227
21. Gazmuri RJ, Dhliwayo N: From a toilet plunger to head-up CPR; bundling systemic and regional venous return augmentation to improve the hemodynamic efficacy of chest compressions. *Resuscitation* 2020; 149:225–227
22. Moore JC, Pepe PE, Scheppke KA, et al: Head and thorax elevation during cardiopulmonary resuscitation using circulatory

adjuncts is associated with improved survival. *Resuscitation* 2022; 179:9–17

23. Moore JC, Holley JE, Frascone RJ, et al: Consistent head-up cardiopulmonary resuscitation haemodynamics are observed across porcine and human cadaver translational models. *Resuscitation* 2018; 132:133–139
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; 377:301–311
25. 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
26. Plaisance P, Soleil C, Lurie KG, et al: 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
27. Wolcke BB, Mauer DK, Schoefmann MF, 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
28. Frascone RJ, Wayne MA, Swor RA, 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
29. Debaty G, Shin SD, Metzger A, et al: Tilting for perfusion: Head-up position during cardiopulmonary resuscitation improves brain flow in a porcine model of cardiac arrest. *Resuscitation* 2015; 87:38–43
30. Moore JC, Salverda B, Lick M, et al: Controlled progressive elevation rather than an optimal angle maximizes cerebral perfusion pressure during head up CPR in a swine model of cardiac arrest. *Resuscitation* 2020; 150:23–28
31. Rojas-Salvador C, Moore JC, Salverda B, et al: Effect of controlled sequential elevation timing of the head and thorax during cardiopulmonary resuscitation on cerebral perfusion pressures in a porcine model of cardiac arrest. *Resuscitation* 2020; 149:162–169
32. Putzer G, Braun P, Martini J, et al: Effects of head-up vs. supine CPR on cerebral oxygenation and cerebral metabolism—A prospective, randomized porcine study. *Resuscitation* 2018; 128:51–55
33. Huang CC, Chen KC, Lin ZY, et al: The effect of the head-up position on cardiopulmonary resuscitation: A systematic review and meta-analysis. *Crit Care* 2021; 25:376
34. Pepe PE, Scheppke KA, Antevy PM, et al: Confirming the clinical safety and feasibility of a bundled methodology to improve cardiopulmonary resuscitation involving a head-up/torso-up chest compression technique. *Crit Care Med* 2019; 47:449–455
35. Moore JC, Duval S, Lick C, et al: Faster time to automated elevation of the head and thorax during cardiopulmonary resuscitation increases the probability of return of spontaneous circulation. *Resuscitation* 2022; 170:63–69
36. Pepe PE, Aufderheide TP, Lamhaut L, et al: Rationale and strategies for development of an optimal bundle of management for cardiac arrest. *Crit Care Explor* 2020; 2:e0214
37. Aufderheide TP, Nichol G, Rea TD, et al; Resuscitation Outcomes Consortium (ROC) Investigators: A trial of an impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med* 2011; 365:798–806
38. Aufderheide TP, Kudenchuk PJ, Hedges JR, et al; ROC Investigators: Resuscitation Outcomes Consortium (ROC) PRIMED cardiac arrest trial methods part 1: Rationale and methodology for the impedance threshold device (ITD) protocol. *Resuscitation* 2008; 78:179–185
39. Geocadin RG, Callaway CW, Fink EL, et al; American Heart Association Emergency Cardiovascular Care Committee: Standards for studies of neurological prognostication in comatose survivors of cardiac arrest: A scientific statement from the American Heart Association. *Circulation* 2019; 140:e517–e542
40. Thomas L, Li F, Pencina M: Using propensity score methods to create target populations in observational clinical research. *JAMA* 2020; 323:466–467
41. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28:3083–3107
42. Andersen LW, Grossestreuer AV, Donnino M: Resuscitation time bias — A unique challenge for observational cardiac arrest research. *Resuscitation* 2018; 125:79–82
43. Moore JC, Pepe PE, Bachista K, et al: Carry less, do more: Properly implementing a basic life support approach to the head-up CPR bundle of care. *EMS World* 2021; 50:2–6
44. Paiva EF, Paxton JH, O'Neil BJ: The use of end-tidal carbon dioxide (ETCO2) measurement to guide management of cardiac arrest: A systematic review. *Resuscitation* 2018; 123:1–7
45. Scheppke K, Pepe PE, Antevy P, et al: Safety and feasibility of an automated patient positioning system for controlled sequential elevation of the head and thorax during cardiopulmonary resuscitation. *Prehosp Emerg Care* 2020; 24:122–123
46. Debaty G, Duhem H, Labarère J, et al: Neuroprotective cardiopulmonary resuscitation to improve outcomes of out-of-hospital cardiac arrest. *Acad Emerg Med* 2023; 30:120
47. McVaney KE, Pepe PE, Maloney LM, et al; writing group on behalf of the Metropolitan EMS Medical Directors Global Alliance: The relationship of large city out-of-hospital cardiac arrests and the prevalence of COVID-19. *EClinicalMed* 2021; 34:e100815
48. Pepe PE, Copass MK, Sopko G: Clinical trials in the out-of-hospital setting: Rationale and strategies for successful implementation. *Crit Care Med* 2009; 37:S91–101
49. Yannopoulos D, Aufderheide TP, Abella BS, et al: Quality of CPR: An important effect modifier in cardiac arrest clinical outcomes and intervention effectiveness trials. *Resuscitation* 2015; 94:106–113
50. Duval S, Pepe PE, Goodloe JM, et al: Optimal combination of compression rate and depth during cardiopulmonary resuscitation to achieve favorable neurological survival. *JAMA Cardiol* 2019; 4:900–908
51. Moore JC, Segal N, Debaty G, et al: The "do's and don'ts" of head up CPR: Lessons learned from the animal laboratory. *Resuscitation* 2018; 129:e6–e7