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Clinical paper

Effect of initial airway strategy on time to epinephrine administration in patients with out-of-hospital cardiac arrest

Joshua R. Lupton[a,*], Robert Schmicker[b], Mohamud R. Daya[a], Tom P. Aufderheide[c], Shannon Stephens[d], Nancy Le[a], Susanne May[b], Juan Carlos Puyana[e], Ahamed Idris[f], Graham Nichol[b], Henry Wang[g], Matt Hansen[a]

[a] Oregon Health and Science University United States
[b] University of Washington United States
[c] Medical College of Wisconsin United States
[d] University of Alabama at Birmingham United States
[e] University of Pittsburgh United States
[f] University of Texas Southwestern United States
[g] University of Texas Health Science Center United States

Abstract

Introduction: Epinephrine and advanced airway management are commonly used during treatment of out-of-hospital cardiac arrest (OHCA). Recent studies suggest that early but not late administration of epinephrine is associated with improved survival. The purpose of this study was to evaluate the effect of initial airway strategy on timing to the first epinephrine dose in OHCA.

Methods: This is a secondary analysis of patients enrolled in the Pragmatic Airway Resuscitation Trial who had an advanced airway attempted. We examined differences in time to epinephrine administration by randomly assigned airway strategy, laryngeal tube (LT) or endotracheal tube (ETI); by the duration of airway attempt; and by number of attempts. We used survival methods to account for interval censoring due to unknown administration time. We also examined the association of epinephrine administration timing with survival to hospital discharge.

Results: Among 2652 subjects (1299 ETI and 1353 LT), 2579 received epinephrine.There were no significant differences between ETI and LT in median time to initial epinephrine administration (min) (ETI – 9.0 vs. LT – 8.6, $p = 0.55$). There was no significant association between the duration of airway attempt or number of attempts and time to initial epinephrine administration ($p = 0.12$ and 0.66, respectively). Early administration of epinephrine (<10 min from EMS arrival) was significantly associated with survival compared to administration ≥10 min (OR 1.36, 95% CI: 1.05, 1.77).

Conclusions: There was no significant association between airway strategy and time to initial epinephrine administration. Earlier administration of epinephrine (< 10 min from EMS arrival) was associated with improved survival.

Keywords: Out-of-hospital cardiac arrest, Epinephrine, Airway management, Supraglottic, Endotracheal

* Corresponding author at: Department of Emergency Medicine, Oregon Health and Science University United States.
E-mail addresses: lupton@ohsu.edu (J.R. Lupton), rschmick@uw.edu (R. Schmicker), dayam@ohsu.edu (M.R. Daya), taufderh@mcw.edu (T.P. Aufderheide), swstephens@uabmc.edu (S. Stephens), lena@ohsu.edu (N. Le), sjmay@uw.edu (S. May), puyanajj@upmc.edu (J.C. Puyana), aidris@sbcglobal.net (A. Idris), nichol@uw.edu (G. Nichol), henry.e.wang@uth.tmc.edu (H. Wang), hansemat@ohsu.edu (M. Hansen).
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Introduction

Survival from out-of-hospital cardiac arrest (OHCA) in the United States has improved over the last two decades, but remains low.[1,2] There have been a limited number of proven treatments beyond cardiopulmonary resuscitation (CPR) and defibrillation for improving OHCA survival.[3] Epinephrine has been long-used to treat OHCA and continues to be recommended in current resuscitation guidelines.[4] Although epinephrine has been associated with higher rates of return of spontaneous circulation (ROSC), admission to hospital, and survival to hospital discharge, it has also been associated with worsened neurological function among survivors.[5–8] However, observational studies from both in-hospital and out-of-hospital cardiac arrest have suggested that timing to the initial dose of epinephrine may be critical for efficacy since early administration has been associated with improved survival.[9–14]

Given that timing to epinephrine administration may be a critical factor in the efficacy of epinephrine and thus the survival from OHCA, it is important to evaluate aspects of the resuscitation effort that may impact the timing of the initial dose of epinephrine. In addition to epinephrine, airway management is a common Advanced Life Support (ALS) intervention during OHCA resuscitation. Advanced airway options include endotracheal intubation (ETI) as well as supraglottic airway devices (SGA) such as the i-gel™ or the King laryngeal tube (LT). Placement of these airways may have an impact on the timing of epinephrine by consuming resources of the resuscitation team and distracting from other priorities. A recent cluster randomized controlled trial, the Pragmatic Airway Resuscitation Trial (PART), demonstrated that an initial strategy of LT use improved survival compared to an initial strategy of ETI in OHCA.[15]

In PART, initial LT use was associated with fewer insertion attempts, greater first attempt success, and shorter intervals to emergency medical services (EMS) first airway attempt compared to ETI.[15] These differences in survival could also be due, in part, to differences in time to initial epinephrine administration. We hypothesized that LT may require less time to insert as compared to ETI, and thus facilitate more timely administration of epinephrine. We also hypothesized that earlier epinephrine would be associated with improved 72-h survival. The objectives of this study were to evaluate the effects of earlier epinephrine on 72-h survival as well as the association between the initial airway strategy used (ETI versus LT) and the timing of initial epinephrine administration among participants of PART.

Methods

Design and setting

We conducted a secondary analysis of data from PART. The methods of the PART trial have previously been reported.[16] Briefly, PART included 27 EMS agencies in Alabama, Dallas-Fort Worth, Milwaukee, Pittsburgh, and Portland. Subjects included in the original trial were adults (age ≥18 years) with non-traumatic OHCA treated by participating EMS agencies. The trial utilized cluster randomization with crossover at 3–5 month intervals.

Intervention

The randomized interventions in the trial were either an initial strategy of LT insertion (intervention arm) or initial strategy of ETI insertion (control arm) for airway management. There were no predetermined limits on the number of initial LT or ETI insertion attempts or restrictions on the type of the rescue airway that the EMS agencies could use if the initial attempt failed. The trial did not dictate or prescribe clinical care at receiving hospitals. In two locations, LT insertion was permitted for basic life support (BLS) providers, who could not administer epinephrine, or perform ETI.

Key variables

Two key variables for this study are time to epinephrine and to first airway attempt measured from initial EMS arrival on scene. We used times recorded in the EMS patient care report to determine these times. We believe that time of arrival on scene is accurate as this is typically recorded by computerized EMS resource tracking systems through dispatch. Careful recording of the timing of the initial airway attempt was emphasized during the EMS training for PART. Due to the pragmatic nature of the trial, we did not standardize the method of recording but instead chose to focus on key variables such as time for first attempt, time to successful placement and confirmation, number of attempts and time that airway attempts were abandoned. Agencies used a variety of methods to record these times including worksheets as well as time stamps on patient monitors in some instances. These methods have been used to determine timing of EMS interventions in other ROC randomized controlled trials for OHCA.[13] All variables used in the analysis were abstracted and entered into an electronic database by trained research assistants at each site. Audits were carried out regularly at each site and agency to ensure data consistency and quality.

Outcomes

Our focus in this analysis was to evaluate the association between advanced airway types and time to first epinephrine administration. Thus, time to initial epinephrine administration from EMS arrival on scene was the primary outcome for this analysis. The primary outcome for PART was 72-h survival after OHCA with secondary outcomes including ROSC, survival to hospital discharge, and favorable neurologic status (Modified Rankin Scale score ≤ 3) at hospital discharge. For a secondary analysis examining survival differences between early and late epinephrine administration, the primary outcome from the original PART analysis, 72-h survival, was used.

Analysis

Utilizing an intention-to-treat approach, we compared the timing to initial epinephrine based on randomization group (LT or ETI). To avoid bias from excluding patients who did not receive epinephrine during resuscitation, we used survival analysis techniques. In addition to right censoring, data could be interval censored if time of epinephrine administration and/or time of first EMS arrival were missing. Median time to epinephrine administration was obtained through Kaplan–Meier analysis. Stratification was done by whether epinephrine was administered before or after the airway was attempted and tested via the Fleming–Harrington test for interval censored data via permutations.[17] To account for potential confounding, we used multivariable Cox regression, adjusting for: age (continuous); sex (male, female, unknown), first recorded EMS rhythm grouped as ventricular fibrillation (VF)/ventricular tachycardia (VT)/shockable by automated external defibrillator, pulseless electrical activity (PEA), asystole, no shock, and no strip (cannot determine); witness status (EMS, bystander, none, unknown); bystander CPR status (no CPR, CPR but no automated external defibrillator (AED), CPR and AED); dispatch to arrival time (continuous); arrest location (public, private); ALS first arrival (yes, no); successful intravenous (IV) or intraosseous (IO) access (neither, IV only, IO only, both); and epinephrine before airway (yes, no). Patients who received no epinephrine were coded as having airway placement before epinephrine administration.

Exploratory analyses examined separately the association of duration of airway attempt and number of airway attempts with time to epinephrine administration. The association between timing of epinephrine administration and survival to hospital discharge was also examined, using a ten-minute cutoff (i.e., $\leq$ 10 min versus $>$ 10 min).

Patients who received BVM-only during resuscitation were specifically excluded from this analysis, as it was felt this patient population was different than those who were treated with advanced airways. In many instances, BVM-only patients had already experienced ROSC before the EMS crew could attempt an advanced airway. We additionally examined differences in the defined subgroups of shockable and non-shockable initial EMS rhythms.

Results

Of 3004 subjects enrolled in PART, 2652 (1299 ETI and 1353 LT) had attempted insertion of an advanced airway (Fig. 1). Patient characteristics by initial airway attempted are listed in Table 1. There were no significant differences between groups with respect to age, sex, initial rhythm, witnessed status, bystander CPR, and arrest location.

There were significant differences in EMS response time ($p < 0.001$) and epinephrine administration ($p < 0.05$), but not type of access (IV or IO) between the LT and ETI groups (Table 2). In addition, there was a significantly ($p < 0.001$) higher rate of overall airway success (94.2%) in the LT group than the ETI group (91.5%) while LT had a significantly ($p < 0.001$) shorter time to airway success from start of airway attempt (0.6 min) compared to ETI (1.2 min). The ETI group had a lower proportion of first pass success than the LT group. Median time from EMS arrival to start of airway attempt was significantly different ($p < 0.001$) between the two groups (LT – 9.0 min, ETI – 11.7 min).

Overall survival for this subgroup of PART subjects was similar to the complete cohort (Table 3). In multivariate logistic regression, early epinephrine (<10 min) compared to late administration (>10 min) was also associated with significantly improved 72-h survival (OR 1.36, 95% CI: 1.05, 1.77).

Epinephrine was administered to 2579 subjects (1272 ETI, 1307 LT) of whom 2404 (1176 ETI, 1228 LT) had a known time from EMS arrival to epinephrine. The median time to epinephrine (95% CI) between the ETI and LT groups was 9.0 min (8.9, 9.4) and 8.6 min (8.3, 9.0), respectively (p = ns) (Table 4). Among those receiving epinephrine prior to the beginning of the airway attempt (n = 1420), there was a small statistically significant difference to epinephrine in the ETI group (8.1 min, 95% CI 8.0, 8.6) compared to the LT group (7.3 min, 95% CI 7.0, 7.6) ($p < 0.001$) (Fig. 2). Among those receiving epinephrine after

Table 1 – Baseline patient characteristics.

	ETI	LT
N	1299	1353
Age[a]		
Median (IQR)	64.0 (23.0)	64.0 (23.0)
Sex[b]		
Male, n (%)	780 (60.0%)	846 (62.5%)
Female, n (%)	519 (40.0%)	505 (37.3%)
Initial rhythm		
VT/VF, n (%)	214 (16.5%)	253 (18.7%)
PEA, n (%)	272 (20.9%)	287 (21.2%)
Asystole, n (%)	668 (51.4%)	667 (49.3%)
No shock advised, n (%)	128 (9.9%)	133 (9.8%)
Cannot determine, n (%)	17 (1.3%)	13 (1.0%)
Witness status		
EMS, n (%)	146 (11.2%)	143 (10.6%)
Bystander, n (%)	458 (35.3%)	461 (34.1%)
None, n (%)	606 (46.7%)	615 (45.5%)
Unknown, n (%)	89 (6.9%)	134 (9.9%)
Bystander resuscitation		
No bystander CPR, n (%)	649 (50.0%)	661 (48.9%)
Bystander CPR, No AED, n (%)	496 (38.2%)	485 (35.8%)
Bystander CPR and AED, n (%)	117 (9.0%)	144 (10.6%)
Unknown, n (%)	37 (2.8%)	63 (4.7%)
Public location, n (%)	152 (11.7%)	133 (9.8%)
Site		
A, n (%)	367 (28.3%)	432 (31.9%)
B, n (%)	57 (4.4%)	65 (4.8%)
C, n (%)	168 (12.9%)	262 (19.4%)
D, n (%)	178 (13.7%)	99 (7.3%)
E, n (%)	529 (40.7%)	495 (36.6%)

Abbreviations: ETI = endotracheal intubation, LT = King laryngeal tube, IQR = interquartile range, VT = ventricular tachycardia, VF = ventricular fibrillation, PEA = pulseless electrical activity, EMS = emergency medical services, CPR = cardiopulmonary resuscitation, AED = automated external defibrillator.
[a] Age was unknown for 2 patients.
[b] Sex was unknown for 2 patients.

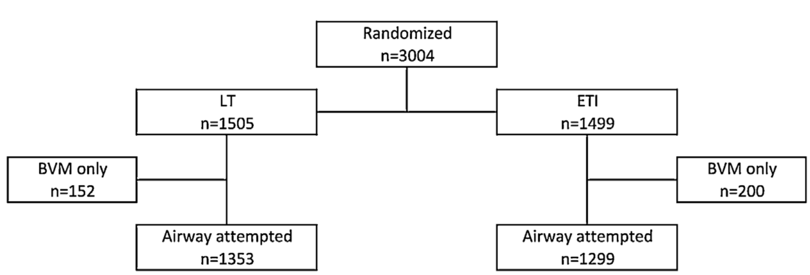

Fig. 1 – Consort diagram for the subjects included in this study.

Table 2 – EMS response characteristics.

	ETI	LT
N	1299	1353
Response time, min		
Median (IQR)	5.3 (2.7)	5.0 (2.5)
<6 min, n (%)	790 (64.3%)	917 (70.6%)
ALS first responder, n (%)	761 (58.6%)	908 (67.1%)
Epinephrine administration		
Administered, n (%)	1272 (97.9%)	1307 (96.6%)
Not administered, n (%)	27 (2.1%)	46 (3.4%)
IV/IO access		
Successful IV access, n (%)	655 (50.4%)	647 (47.8%)
Successful IO access, n (%)[a]	690 (53.1%)	760 (56.2%)
Airway successful, n (%)	1188 (91.5%)	1275 (94.2%)
Time from airway attempt to success, min		
Known time, n	954 (80.3%)	1061 (83.2%)
Median (IQR)	1.2 (3.5)	0.6 (1.0)
Time from airway attempt to abandonment, min		
Known time, n	56 (50.5%)	49 (62.8%)
Median (IQR)	1.0 (4.0)	1.1 (3.0)
Time from airway attempt to success or abandonment, min		
Known time, n	1014 (78.1%)	1109 (82.0%)
Median (IQR)	1.2 (3.5)	0.7 (1.1)
Airway attempts		
1, n (%)	695 (53.5%)	1135 (83.9%)
2, n (%)	359 (27.6%)	157 (11.6%)
3 or more, n (%)	245 (18.9%)	61 (4.5%)
Median (IQR)	1.0 (1.0)	1.0 (0.0)

Abbreviations: EMS = emergency medical services ETI = endotracheal intubation, LT = King laryngeal tube, IQR = interquartile range, ALS = advanced life support, IV = intravenous, IO = intraosseous.
[a] IO site location unknown.

the airway attempt had begun (n = 663), there was also a small statistically significant difference in time to epinephrine between the ETI group (10.9 min, 95% CI: 10.1, 11.6) and the LT group (10.1 min, 95% CI: 9.9, 11.0) (p = 0.03).

When adjusted for covariates, the probability of epinephrine administration was 8% higher in the LT group than the ETI group (hazard ratio (HR) = 1.08, 95% CI: 0.99, 1.19) at any time point in the resuscitation effort. In separate analyses examining the association of duration of airway attempt and number of attempts (one, two, or greater than three) on time to epinephrine administration, there were no significant differences in the probability of epinephrine administration at any time point (Table 4).

In subgroup analysis, the median time to epinephrine administration (95% CI) was similar for ETI compared to LT for an initial rhythm of PEA/asystole (ETI at 9.0 min (8.7, 9.4) versus LT at 8.6 min (8.3, 9.0), p = ns) and also for an initial rhythm of VT/VF (ETI at 9.0 min (8.5, 9.6) versus LT at 8.0 min (7.6, 8.4), p = ns) (Table 4). In the group of patients that had an airway attempt prior to epinephrine administration, the absolute difference across randomization arms in the VT/VF subgroup (ETI at 10.8 min versus LT at 9.1 min) compared to the PEA/asystole subgroup (ETI at 10.9 min versus LT at 10.8 min) was similar (p = 0.11 and p = 0.08, respectively).

Discussion

The initial airway strategy of ETI compared to LT, duration of airway attempt, and number of airway attempts were not associated with any statistically significant difference in time to initial epinephrine administration. However, when subjects were stratified by whether epinephrine was given before versus after the airway attempt, epinephrine was administered more quickly in the LT group compared to the ETI group. It remains possible that for a subset of patients, airway strategy affects timing to epinephrine administration. There was no difference in time to administration in the LT group compared to the ETI group in the subset of patients presenting with VT/VF as the initial rhythm, possibly due to the small sample size of this subgroup. We infer that airway strategy choice may have a greater effect on team resources in subjects with shockable rhythms in whom the responding personnel must balance the need for timely defibrillation in addition to high quality CPR, vascular (IV or IO) access, drug administration, and airway management.

Among our cohort of 2404 subjects with cardiac arrest in whom the time to epinephrine was known, there were greater odds of 72-h survival if epinephrine was administered in less than 10 min compared

Table 3 – Outcomes by epinephrine administration time.

	Endotracheal intubation	Laryngeal tube
n	1299	1353
ROSC in-field, n (%)	419 (32.3%)	500 (37.0%)
epinephrine ≥ 10 min	141 (27.9%)	185 (36.9%)
epinephrine < 10 min	253 (34.5%)	301 (37.6%)
ROSC at ED arrival, n (%)	307 (23.6%)	359 (26.5%)
epinephrine ≥ 10 min	100 (19.8%)	128 (25.5%)
epinephrine < 10 min	187 (25.5%)	224 (28.0%)
Transport to ED, n (%)	776 (59.7%)	802 (59.3%)
epinephrine ≥ 10 min	284 (56.2%)	296 (59.0%)
epinephrine < 10 min	443 (60.4%)	483 (60.4%)
Admitted to hospital, n (%)	303 (23.3%)	360 (26.6%)
epinephrine ≥ 10 min	108 (21.4%)	125 (24.9%)
epinephrine < 10 min	182 (24.8%)	224 (28.0%)
Survival to 72 h, n (%)	174 (13.4%)	218 (16.1%)
epinephrine ≥ 10 min	55 (10.9%)	67 (13.3%)
epinephrine < 10 min	112 (15.3%)	145 (18.1%)
Survival to hospital discharge, n (%)	75 (5.8%)	109 (8.1%)
epinephrine ≥ 10 min	27 (5.3%)	37 (7.4%)
epinephrine < 10 min	45 (6.1%)	70 (8.8%)
MRS ≤ 3 at discharge, n (%)	40 (3.1%)	61 (4.5%)
epinephrine ≥ 10 min	15 (3.0%)	23 (4.6%)
epinephrine < 10 min	24 (3.3%)	38 (4.8%)

Abbreviations: ROSC = return of spontaneous circulation, MRS = Modified Rankin Scale.

Table 4 – Timing to epinephrine.

	Endotracheal intubation			Laryngeal tube		
	Overall	Before airway	After airway	Overall	Before airway	After airway
All initial rhythms						
n	1176	770	239	1228	650	424
Arrival to Epi administration time, median (95% CI)	9.0 (8.9, 9.4)	8.1 (8.0, 8.6)	10.9 (10.1, 11.6)	8.6 (8.3, 9.0)	7.3 (7.0, 7.6)	10.1 (9.9, 11.0)
Initial rhythm VT/VF						
n	195	127	42	227	122	74
Arrival to Epi administration time, median (95% CI)	9.0 (8.5, 9.6)	8.2 (7.3, 9.1)	10.8 (9.0, 12.7)	8.0 (7.6, 8.4)	7.4 (7.0, 7.8)	9.1 (8.0, 10.0)
Nonshockable initial rhythm						
n	861	634	194	880	524	344
Arrival to Epi administration time, median (95% CI)	9.0 (8.7, 9.4)	8.1 (9.0, 8.5)	10.9 (10.1, 11.7)	8.6 (8.3, 9.0)	7.4 (7.0, 7.8)	10.8 (10.0, 11.5)

Abbreviations: ETI = endotracheal intubation, LT = King laryngeal tube, VT = ventricular tachycardia, VF = ventricular fibrillation, PEA = pulseless electrical activity.

to 10 min or greater. This is similar to the associated survival benefit previously published from the ROC Epistry,[13] and supports the notion that earlier epinephrine administration may be associated with improved survival. However, there are also other studies that have failed to demonstrate survival benefits from earlier epinephrine administration.[18,19] This may be due, in part, to a harmful effect on survival if epinephrine is given too early in a resuscitation when ROSC would have been readily achieved with high quality CPR and timely defibrillation.[20]

Animal models have shown that epinephrine administration increases mean aortic pressure and is associated with significantly increased rates of ROSC but additionally is associated with decreased microcirculatory brain flow and with post-ROSC myocardial dysfunction.[21,22] It may be that as the duration of cardiac arrest increases and

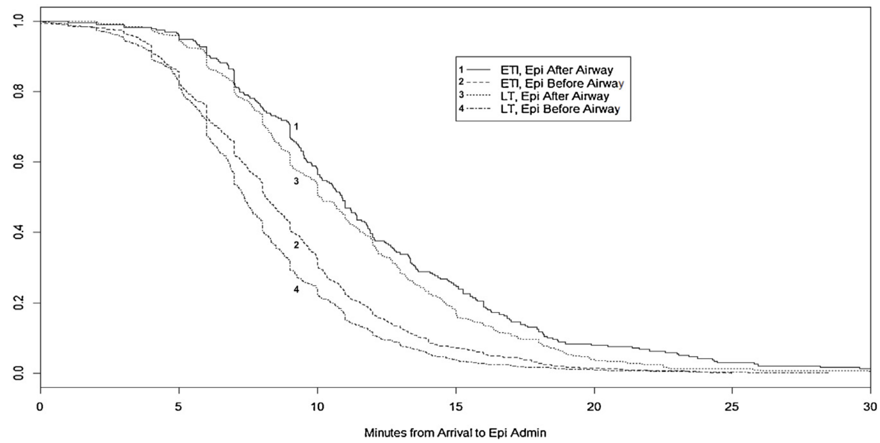

Fig. 2 – Kaplan-Meier analysis of randomized airway effect on time to epinephrine stratified by those receiving epinpehrine before compared to after airway attempt.

there is worsened ischemic damage to the brain, the microcirculatory hypoperfusion from epinephrine has a greater detrimental effect on neurologically intact survival than if given earlier in the resuscitation. Similar multi-stage models of cardiac arrest have been proposed and suggest that the circulatory phase in which vasoconstrictors would be most efficacious was anywhere from four to fifteen minutes after OHCA.[23,24] This further emphasizes that the efficacy of OHCA interventions need to be examined in the time-course that they are expected to be most beneficial.

Limitations

This study had limitations similar to those in the parent trial.[15] We lacked data on epinephrine timing for the entire study cohort. As previously reported, the initial success rates for ETI were low in this study (51% in the overall cohort) and it is possible that higher overall initial ETI success would affect the timing to epinephrine, though in our study there were no associations between airway attempt duration or number of attempts and timing to epinephrine. The time to epinephrine was also not uniformly recorded using the same methods, though this should have affected both randomized groups equally. As in the original study, we did not have data on CPR quality, which could have given further insight into the hypothesis that airway choice may distract from other critical aspects of resuscitation. There was also no standardization of route of epinephrine administration between IO and IV. Rates of IO use were similar between groups, and the most commonly used IO site was the proximal tibia, though no detailed data on IO placement site were collected. It is possible that one location or route affords more rapid administration of epinephrine in a way that biased our findings. Additionally, the study used LTs specifically and did not examine other SGAs. These results only pertain to the OHCA environment and not the in-hospital setting. Finally, our findings may not be generalizable to EMS systems where passive oxygen insufflation or BVM only are primarily used to manage the airway in OHCA.

Conclusions

There was no significant association between airway strategy and time to initial epinephrine administration in PART. Earlier administration of epinephrine (<10 min from EMS arrival) was associated with improved survival.

Conflict of interest

Dr. Wang received grants from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) and provided research consultation for Shire Inc. Mr. Schmicker; Drs. Daya, Aufderheide, and May reported receiving grants from the NHLBI. Dr. Idris reported receiving grants from the NIH, University of Alabama, and HeartSine Inc and being an uncompensated member of HeartSine Inc's scientific advisory board. Dr. Nichol reported receiving salary support from Medic One Foundation; grants from NIH, Agency for Healthcare Research and Quality, and U.S. Food and Drug Administration; and contracts from Abiomed, GE Healthcare, and ZOLL Medical Corp, and providing consultancy to ZOLL Circulation. All other authors report no conflicts of interest.

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