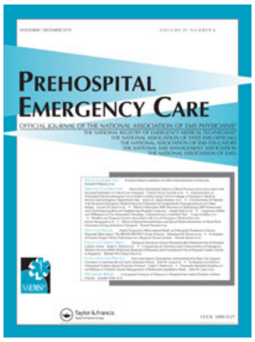

Prehospital Emergency Care

ISSN: 1090-3127 (Print) 1545-0066 (Online) Journal homepage: https://www.tandfonline.com/loi/ipec20

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Focus on Cardiac Arrest

Timing of Advanced Airway Placement after Witnessed Out-of-Hospital Cardiac Arrest

Justin L. Benoit, MD, MS, Jason T. McMullan, MD, Henry E. Wang, MD, MPH, MS, Changchun Xie, PhD, Peixin Xu, MS, Kimberly W. Hart, MA, Uwe Stolz, PhD, MPH, Christopher J. Lindsell, PhD

Abstract

Background: Advanced airways (endotracheal tubes, supraglottic airways) are frequently placed by Emergency Medical Services (EMS) in patients with out-of-hospital cardiac arrest (OHCA). However, if an airway is to be placed, it is unknown whether this should occur early or late in the sequence of resuscitation events. This study evaluated the association between the timing of airway placement and the minute-to-minute probability of achieving return of spontaneous circulation (ROSC). **Methods:** This secondary analysis of Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance Valve and Early versus Delayed (ROC PRIMED) study data included adult, non-traumatic, witnessed OHCA patients with airway placement by EMS before ROSC. The primary exposure variable was time from EMS arrival to advanced airway placement. The outcome was prehospital ROSC. Since resuscitations occur over time, a Cox proportional hazards model was fit to estimate the probability of ROSC as a function of the airway timing, adjusting for Utstein variables. **Results:** A total of 7,547 patients were included. Time to airway placement was 0–5 minutes in 12% of the cohort, >5–10 (36%), >10–15 (29%), >15–20 (14%), >20–25 (5%), >25–30 (2%), and >30 (2%). ROSC occurred in 43%. Time to airway had a statistically significant impact on ROSC. A negative association between the time to airway placement and the hazard of ROSC was observed, such that increasing intervals between EMS arrival and airway placement were associated with decreasing probabilities of ROSC, regardless of initial cardiac rhythm. **Conclusions:** EMS advanced airway placement has a time-dependent association with ROSC. In witnessed OHCA patients receiving advanced airways, early airway placement is associated with increased probability of ROSC. **Key words:** cardiac arrest; advanced cardiac life support; endotracheal intubation; supraglottic airway; emergency medical services; prehospital

PREHOSPITAL EMERGENCY CARE 2019;23:838–846

Received January 24, 2019 from Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio (JLB, JTM, US); Department of Emergency Medicine, University of Texas Health Science Center at Houston, Houston, Texas (HEW); Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio (CX, PX); Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee (KWH, CJL). Revision received March 5, 2019; accepted for publication March 11, 2019.

American Heart Association's Resuscitation Science Symposium (November 2017, Anaheim, USA)

National Association of EMS Physicians (January 2018, San Diego, USA)

J.L. Benoit, J.T. McMullan, and C.J. Lindsell conceived the study and designed the trial. J.L. Benoit, J.T. McMullan, H.E. Wang, and C.J. Lindsell obtained research funding. C. Xie, P. Xu, K.W. Hart, U. Stolz, and C.J. Lindsell provided statistical advice on study design and analyzed the data. All authors contributed substantially to the manuscript. J.L. Benoit takes responsibility for the paper as a whole.

This work was supported by the Society for Academic Emergency Medicine Foundation under Grant RF2015-001, and the Cincinnati Center for Clinical and Translational Science and Training under Grant CTSA 5-UL1-TR001425-02.

The authors report no conflicts of interest.

Supplemental material for this article can be accessed on the publisher's website.

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doi:10.1080/10903127.2019.1595236

Introduction

Every year in the United States, approximately 395,000 people suffer out-of-hospital cardiac arrest (OHCA), and only 11% of patients who undergo resuscitative efforts survive to hospital discharge (1). Interventions performed by Emergency Medical Services (EMS) can significantly improve the chance of survival. Survival is 17% with prehospital return of spontaneous circulation (ROSC) but only 1% when ROSC is achieved after hospital arrival (2). EMS providers must prioritize competing intra-arrest interventions, such as chest compressions, defibrillation, vascular access, medication administration, oxygenation/ventilation, and airway management. Advanced life support guidelines attempt to specify the optimal timing of interventions during the sequence of resuscitation events (3, 4). Advanced airways, such as endotracheal tubes and supraglottic airways, are placed in 80% of OHCA patients (5–7). However, when an advanced airway is indicated, the optimal timing for its placement is unknown and remains unspecified in guidelines (3, 4).

Advanced airways may improve survival by the early reversal of hypoxemia and acidosis, which may be a cause or consequence of OHCA (8). Alternatively, survival may be decreased if airway interventions delay other critical interventions such as defibrillation or chest compressions (9–12). Prior studies on airway timing have either oversimplified the timing of resuscitation events or evaluated in-hospital patients who differ in their pathophysiology (13–17). Thus, a fundamental question remains unanswered: if an advanced airway is to be placed, should it occur early or late in the sequence of resuscitation events?

Our study evaluates the association between the timing of prehospital advanced airway placement and the minute-to-minute probability of achieving ROSC in patients with witnessed OHCA. We hypothesize that in patients for whom an advanced airway is indicated, there is a time after which the importance of placing it outweighs the need for other resuscitation events in maximizing the probability of ROSC.

Methods

Study Design and Setting

This was an observational cohort study using data from the Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation using an Impedance Valve and Early versus Delayed (PRIMED) trial (18, 19). This trial was conducted from June 2007 to July 2010 at 10 academic centers across North America covering 150 different EMS agencies under Exception from Informed Consent (EFIC) regulations in the United States and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans in Canada. Data were available through the National Heart, Lung, and Blood Institute (NHLBI) Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) (20). Our Institutional Review Board designated this study as Not Human Subjects Research as data were de-identified and publicly available.

Data Source

The PRIMED trial enrolled adult, non-traumatic, OHCA patients and evaluated two interventions using a factorial design: (1) immediate versus delayed initial cardiac rhythm analysis, and (2) an impedance threshold device vs. a sham device (18, 19). The study was stopped early due to futility, as no difference in patient outcomes was detected. Of the patients enrolled, 25% arrived at the hospital with ROSC, 8% survived to hospital discharge, and 6% survived to hospital discharge neurologically intact.

Centralized data collection occurred prospectively and was managed by the ROC Data Coordinating Center following uniform data collection and reporting guidelines consistent with Utstein standards (21, 22). The PRIMED dataset contains detailed time information on resuscitation events, including initial emergency phone call, first responder arrival, paramedic arrival, advanced airway placement, ROSC, hospital arrival, and termination of resuscitation. These times were calculated using information from EMS providers on scene, EMS dispatch, and the cardiac monitor. Analyses of these data have been sufficiently accurate to ascribe variation in time between patient groups on the order of seconds (18, 23).

Study Population

We included all patients who received endotracheal intubation or placement of a supraglottic airway by EMS, including patients enrolled during the run-in period of the original trial. The PRIMED trial excluded patients with traumatic etiology of arrest (i.e., drowning, strangulation, electrocution, hanging, lightning, exsanguination), patients <18 years old, and patients with a Do Not Resuscitate order. We excluded unwitnessed arrests, EMS witnessed arrests, and patients who had an advanced airway placed after ROSC. Arrests had to be witnessed so the exact time of disease onset (i.e. cardiac arrest) was known for survival analysis. EMS witnessed arrests were excluded because airway interventions could have occurred prior to disease onset. Since initial resuscitative efforts focus on obtaining ROSC, advanced airways placed after ROSC have a different therapeutic intention.

Exposure, Outcome, and Covariates

The exposure variable was the time from initial EMS arrival to the successful placement of an advanced airway (endotracheal tube or supraglottic

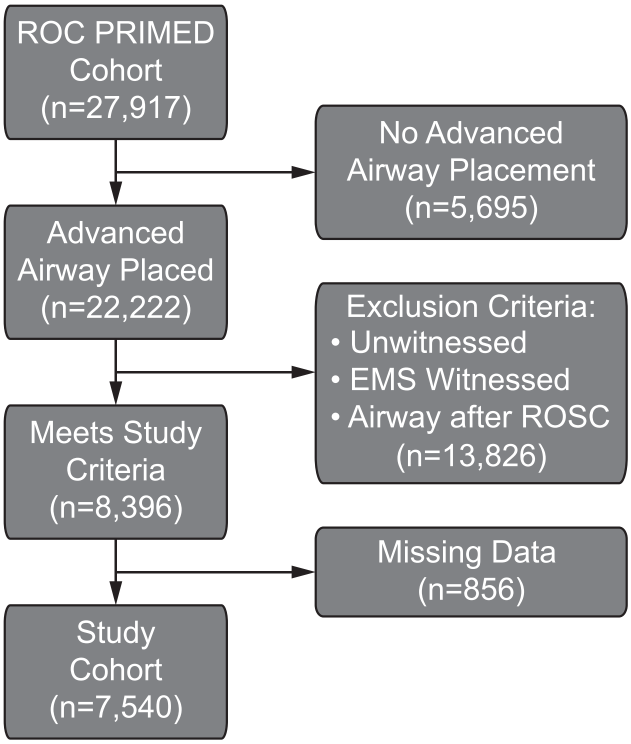

Figure 1. Selection of study population. Flow diagram showing patient selection for the study cohort. ROC PRIMED = *Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance Valve and Early versus Delayed Trial*; EMS = *Emergency Medical Services*; ROSC = *Return of Spontaneous Circulation*.

airway). It is important to note that the exposure variable is the *timing* of advanced airway placement, not the decision to place an advanced airway. Therefore, patients who received only bag-valve mask ventilation were not included.

The outcome variable was the occurrence of prehospital ROSC, defined as a measureable pulse and blood pressure at any time during the prehospital resuscitation. Per the Resuscitation Outcome Consortium, a pulse alone was not sufficient. We specifically chose prehospital ROSC because it is the OHCA outcome most likely to change in response to a time-dependent airway management decision by EMS, and prehospital ROSC is a critical first step towards neurological recovery (2). In addition, using ROSC as the outcome enabled the use of survival analysis to address the confounding effect of the total time in cardiac arrest before ROSC, which is not possible using distal survival outcomes.

Covariates were age, sex, initial cardiac rhythm, presence or absence of bystander cardiopulmonary resuscitation (CPR), and EMS response time, defined as the time from cardiac arrest onset to initial EMS arrival. The earliest recorded time was the initial emergency phone call received at the public-safety answering point. Since all arrests were witnessed, this was used as a surrogate for the time of cardiac arrest onset for calculating EMS response time. Response time was treated as a covariate (not part of the exposure variable) because EMS cannot affect a patient's condition during this time.

Chest compression fraction and bystander automated external defibrillator (AED) use were not used as covariates. Chest compression fraction has been an inconsistent predictor of patient outcomes in multiple studies (24–26). In addition, only 5 minutes of chest compression fraction data were available per patient, which is an inadequate measure of CPR quality for a prolonged resuscitation. Bystander AED use was not considered since successful defibrillation using an AED would have resulted in ROSC prior to EMS arrival and subsequent exclusion from our analysis.

Statistical Model

A Cox proportional hazards model was fit to estimate the probability of ROSC as a function of the time from EMS arrival to advanced airway placement. This differs from standard survival analysis because the exposure variable (time from EMS arrival to advanced airway placement) is *itself* a timed intervention that could vary in the model. The model was specified *a priori* since the goal was to test a theoretical model of the underlying pathophysiology (8). The effect that advanced airway time has on ROSC was unknown, so it was modeled as a continuous variable using cubic splines to allow for non-linear relationships, which fit a comparatively small set of splines and penalized the integrated second derivative (27). Cox models were fit separately for patients with an initial shockable rhythm (ventricular fibrillation, ventricular tachycardia) and those with an initial non-shockable rhythm (pulseless electrical activity, asystole, no shock from EMS AED). This stratification is clinically relevant, as the only branch point in the Advanced Cardiac Life Support algorithm is based on initial cardiac rhythm (4). Utstein covariates (age, sex, bystander CPR, and EMS response time) were included as fixed variables. Time in the model starts at initial EMS arrival. The hazard of ROSC is calculated at any given point in time during the resuscitation, and patients exit the model for one of three reasons: (1) prehospital ROSC, (2) hospital arrival, or (3) prehospital termination of resuscitation. As such, patients contribute to the model throughout their exposure to resuscitation, and this naturally accounts for the duration of the resuscitation in the model (28, 29). Patients were right censored at time of hospital arrival. Termination of resuscitation was modeled as never having the outcome.

Multiple post hoc sensitivity analyses were performed. Survival models were constructed that added impedance threshold device versus sham and the type

TABLE 1. Demographics and resuscitation events

	Study Cohort ($n = 7540$)	Missing Data ($n = 856$)
Age (mean, SD)	67 (15)	66 (15)
Sex (Male, %)	5208 (69.1%)	554 (64.9%)
Bystander Cardiopulmonary Resuscitation (%)		
Yes	3691 (49.0%)	382 (44.6%)
No	3615 (47.9%)	442 (51.6%)
Unknown	234 (3.1%)	32 (3.7%)
Initial Cardiac Rhythm (%)		
Ventricular Tachycardia or Ventricular Fibrillation	2837 (37.6%)	267 (32.4%)
Pulseless Electrical Activity	1906 (25.3%)	231 (28.1%)
Asystole	2251 (29.9%)	234 (28.4%)
No Shock from EMS Automated External Defibrillator	546 (7.2%)	91 (11.1%)
Advanced Airway Attempt (median, IQR)	1 (1–1)	1 (1–1)
Prehospital ROSC (%)	3220 (42.7%)	313 (36.6%)
Prehospital Termination of Resuscitation (%)	2382 (31.6%)	258 (30.1%)
Time to Event (minutes)		
Cardiac Arrest Onset to EMS Arrival Time (median, IQR)	5.6 (4.4–7.0)	5.4 (4.1–7.1)
EMS Arrival to Advanced Airway Time (median, IQR)	10.4 (7.2–14.8)	10.0 (7.0–14.5)
EMS Arrival to Prehospital ROSC Time (median, IQR)	19.2 (14.3–25.2)	18.3 (13.3–25.7)
EMS Arrival to TOR Time (median, IQR)	31.9 (26.7–37.1)	29.0 (24.9–35.0)
EMS Arrival to Hospital Arrival Time (median, IQR)	35.9 (28.9–44.0)	32.9 (26.0–42.0)

SD = *standard deviation*; IQR = *interquartile range*; ROSC = *return of spontaneous circulation*; EMS = *emergency medical services*; TOR = *termination of resuscitation*.

of advanced airway (endotracheal tube versus supraglottic airway) as covariates. Another survival model combined all patients into a single cohort and initial cardiac rhythm was added as a covariate instead of a stratifying variable. Multiple imputation of missing data was performed using chained equations with linear or logistic regression, as appropriate (30). Twenty-five imputations were performed. Finally, logistic regression models were constructed for initial shockable and non-shockable rhythms using survival to hospital discharge and neurologically-intact survival at hospital discharge (Cerebral Performance Category Score $\leq$ 2) as outcomes, with all other covariates included as previously described. Statistical analyses were conducted using SPSS (Version 24, IBM Corporation, Armonk, NY), Stata (Version 15, StataCorp, College Station, TX, USA), R base (3.4.2), and the R package pspline (27, 31).

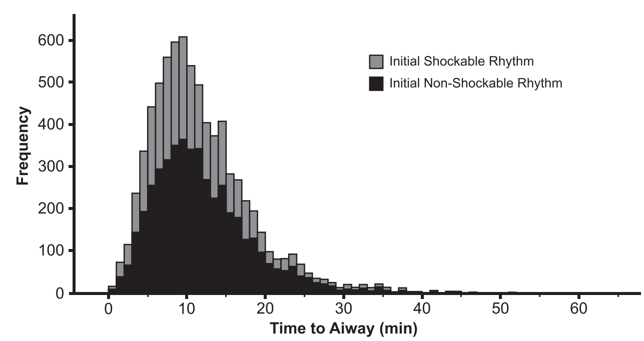

FIGURE 2. Time from Emergency Medical Services (EMS) arrival to advanced airway placement. Histogram of successful advanced airway placement time relative to EMS arrival for the study cohort, stratified by initial cardiac rhythm. Shockable: Ventricular tachycardia or ventricular fibrillation; Non-Shockable: Pulseless electrical activity, asystole, or no shock from EMS automated external defibrillator.

RESULTS

A total of 7,547 patients were available for analysis after applying inclusion/exclusion criteria and accounting for missing data (Figure 1). Demographic and resuscitation data are shown for the study cohort and those with missing data (Table 1). All patients had a bystander witnessed OHCA. The majority of patients had only one attempt at an advanced airway. The median time of advanced airway placement was 10 minutes after EMS arrival (Figure 2). Time to airway placement was 0–5 minutes in 12% of the cohort, >5–10 (36%), >10–15 (29%), >15–20 (14%), >20–25 (5%), >25–30 (2%), and >30 (2%). The primary outcome of prehospital ROSC occurred in 43% of the cohort after a median of 19 minutes of resuscitation. The median resuscitation time for those patients without ROSC and not transported to the hospital was 32 minutes. The number of patients contributing to the model and at risk of ROSC at 5-minute intervals starting from EMS arrival is shown in Table 2.

Model results are shown in Figure 3. Continuous hazard ratios with associated 95% confidence intervals are presented, with the time from EMS arrival to advanced airway placement presented as a continuous exposure variable. A statistically significant negative association between the time to advanced airway placement and the hazard of ROSC was observed, such that increasing intervals between EMS arrival and airway placement were associated with decreasing probabilities of ROSC. This negative association begins immediately and is present regardless of initial cardiac rhythm.

To better illustrate the clinical relevance of these results, 12 independent simulations were run to produce theoretical survival curves estimated from the same model (Figure 4). Since these are independent simulations for specific advanced airway placement times, there are no tests of significance between groups or confidence intervals to report. Times were chosen for illustrative purposes only. Since the outcome is a good patient event (ROSC), not a bad event (death), a drop in the survival curve indicates good patient outcomes. For all simulations, the cumulative probability of achieving ROSC increases as the resuscitation progresses and eventually the cumulative probability plateaus. However, the earlier the advanced airway is placed, the higher the cumulative probability of achieving ROSC. This association is present regardless of initial cardiac rhythm.

Sensitivity analyses of impedance threshold device use, the type of advanced airway, initial cardiac rhythm, and multiple imputation of missing data did not change the overall negative association between the time to advanced airway placement and the hazard of ROSC (Supplemental Figures S1 to S6). A similar association was observed for sensitivity analyses of distal patient outcomes. Each additional minute from EMS arrival to advanced airway placement decreased survival to hospital discharge for initial shockable (adjusted OR 0.91; 95% CI 0.89 to 0.93) and non-shockable rhythms (adjusted OR 0.89; 95% CI 0.85 to 0.92), and also decreased neurologically-intact survival to hospital discharge for initial shockable (adjusted OR 0.93; 95% CI 0.91 to 0.95) and non-shockable rhythms (adjusted OR 0.89; 95% CI 0.82 to 0.95).

TABLE 2. Patients at risk of ROSC

Resuscitation Time (min)	Number at Risk
0	7,540
5	7,520
10	7,289
15	6,561
20	5,485
25	4,298
30	2,940
35	1,746
40	957
45	493
50	254
55	126
60	65
65	35
70	19
75	5
80	4
85	2

ROSC = *return of spontaneous circulation*. The number patients contributing to the model and at risk of ROSC. Resuscitation time begins at the arrival of Emergency Medical Services. Patients exit the model for one of three reasons: (1) prehospital ROSC, (2) hospital arrival, or (3) prehospital termination of resuscitation.

DISCUSSION

In a cohort of witnessed OHCA patients who received intra-arrest advanced airways, earlier placement was associated with a higher probability of achieving ROSC. Current guidelines emphasize the circulatory components of CPR, with a focus on compression fraction, compression rate, and minimizing pauses related to pulse checks and defibrillation (4, 32, 33). As a result, the roles of airway management and ventilation have been relatively minimized or even purposefully eliminated (9, 10). This could lead to delays in advanced airway placement which, based on our data, would limit the efficacy of this particular intervention. Our results suggest that airway management plays a role in OHCA resuscitation efforts and should receive early attention during prehospital care.

It is important to note that the hazard ratios in Figure 3 are monotonically decreasing. If a curvilinear line with a peak had been observed, this would have indicated the existence of a specific time during the resuscitation when advanced airway placement is most favorable in patients for whom an airway is indicated. Times both before and after this would have been expected to negatively impact the probability of achieving ROSC. To illustrate, immediate defibrillation and continuous chest compressions in patients with shockable rhythms are believed to be the most important tasks during resuscitation (34). Multiple studies have argued that advanced airways are harmful because they interrupt these interventions (9–12). We expected to see a delayed peak in the hazard ratio for this group, indicating that delaying airway interventions to conduct defibrillation and continuous chest compressions improves the probability of achieving ROSC. However, this was not observed, which is consistent with prior studies on the timing of advanced airway placement (13–17). This could be because some patients rapidly achieved ROSC after a single defibrillation, or because interventions occurred simultaneously.

Evidence that EMS providers should place advanced airways has been questioned and the practice remains controversial. Multiple studies have focused on the harmful effects of poor airway management (12, 35–37). Although important, harm from poor technique is not the same as harm from the intervention itself. Despite concerns that airway interventions harm patients, recent pathophysiological studies have challenged this dogma, demonstrating improved outcomes with higher airway pressures and have failed to see evidence of respiratory alkalosis from hyperventilation (38, 39). Our study was not designed to provide direct evidence of a benefit of an advanced airway compared to no advanced airway, but the time-dependent relationship in Figure 3 provides supporting evidence that an advanced airway *itself* influences patient outcomes. How this compares to other potential interventions or is impacted by poor procedural technique remains an active area of investigation.

This study also demonstrates a novel methodology for analyzing time-dependent interventions while simultaneously accounting for the total time in cardiac arrest before ROSC. This technique could be applied to the recently released PART and AIRWAYS-2 trial data (40, 41). Although the data source for the present study is almost 10 years old, recommendations for advanced airway management have not changed during that time. Future efforts could also utilize propensity matching to compare patients who received an early vs. late advanced airway, but these efforts must adjust for the confounding effect of the duration of resuscitative efforts (28).

EMS systems performing high-quality CPR often delay advanced airway interventions to focus on chest compressions, so it is unlikely that delayed airway placement is a surrogate for poor resuscitation technique. EMS system-specific data were not available to evaluate differences between sites, and this remains an area for future work. However, significant variation in patient outcomes across these systems has been observed previously, which improves the generalizability of the results (42). Rapid advanced life support was required for participation in the ROC, and patients were excluded from the original trial if a non-ROC EMS agency arrived first (43). The type of advanced airway did not change our overall results, but the comparative effectiveness of different advanced airway devices is better address by two recently published randomized controlled trials (40, 41).

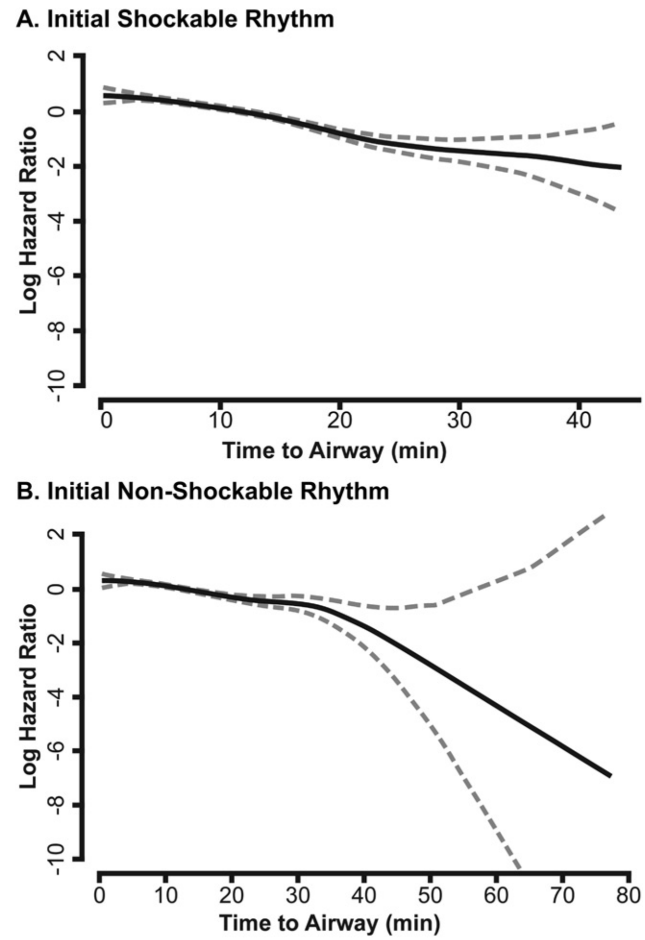

FIGURE 3. Model results. The hazard of prehospital return of spontaneous circulation (ROSC) divided by the baseline hazard (y-axis) at different times from Emergency Medical Services (EMS) arrival to advanced airway placement (x-axis). Dashed lines indicate 95% confidence intervals. The y-axis uses a log scale to better visualize the negative association and has no units because it is a ratio. A value of 0 on the y-axis has no meaning because the intercept was not specified. Separate analyses were conducted based on initial cardiac rhythm. Shockable: Ventricular tachycardia or ventricular fibrillation; Non-Shockable: Pulseless electrical activity, asystole, or no shock from EMS automated external defibrillator

LIMITATIONS

These results do not address the question of whether a bag-valve mask or an advanced airway is better for patient outcomes, because our entire cohort eventually received an advanced airway. Given that 80% of OHCA receive an advanced airway in the United States, we wanted to investigate the *timing* of advanced airway placement, not the decision to place an advanced airway (5). Thus, we did not include patients who were exposed after the outcome had occurred or were never exposed. However, the potential for selection bias exists. Since patients must have had an advanced airway placed prior to ROSC to be included, it is unknown whether patient who did not receive an advanced airway would have had earlier ROSC had one been obtained.

A natural extension of our work might be to include all cardiac arrest patients and assess the relative importance of obtaining an early advanced airway versus no advanced airway. However, this question is limited by confounding by indication. For example, patients with a presumed respiratory etiology of cardiac arrest or patients with vomitus/blood in the airway may be simultaneously more likely to receive an early advanced airway and more likely to never achieve ROSC when compared to a presumed cardiac etiology or patients without aspiration. Confounding by indication is the most likely reason why observational data indicated endotracheal tubes are superior to supraglottic airways, while randomized trial data indicated the opposite, as supraglottic airways are occasionally placed after failed endotracheal intubation (6, 40). If confounding by indication is strong enough to reverse results when two advanced airway methods are compared, confounding may be more problematic when comparing basic to advanced airway methods. We carefully chose the cohort for this study to avoid confounding by indication, which has been a limitation of prior studies (44–46). Unfortunately, the reason why an advanced airway is placed or not is rarely described or recorded, and current cardiac arrest guidelines allow for this variability in clinical practice (4, 32, 33).

Unlike ROSC, the analyses of distal patient outcomes are limited by resuscitation time bias, as we could not use survival analysis since time to survival is not useful in this context. In addition, the number of confounders introduced by using distal outcomes that occur weeks later is challenging to adjust for using observational data. For these reasons, we used ROSC as our main outcome and consider other outcomes to be sensitivity analyses. Unlike epinephrine administration, we are not aware of any data that suggests that the timing of advanced airway placement will have a paradoxical increase in ROSC while decreasing neurologically-intact survival (47).

Additional limitations exist. We excluded unwitnessed arrests because the exact time of disease onset had to be known for survival analysis. Current treatment guidelines for OHCA are unmodified by witness status or time since arrest, as this only affects prognostication (4, 32). However, the generalizability of our results to unwitnessed arrests is unknown. We could not directly address patients who re-arrested after initial prehospital ROSC using this model, as patients exit the model once the outcome is achieved. However, overall results were unchanged by sensitivity analyses of distal survival outcomes. We did not directly address the number of attempts to obtain an advanced airway, and the duration of airway attempts was not available. Although some airway

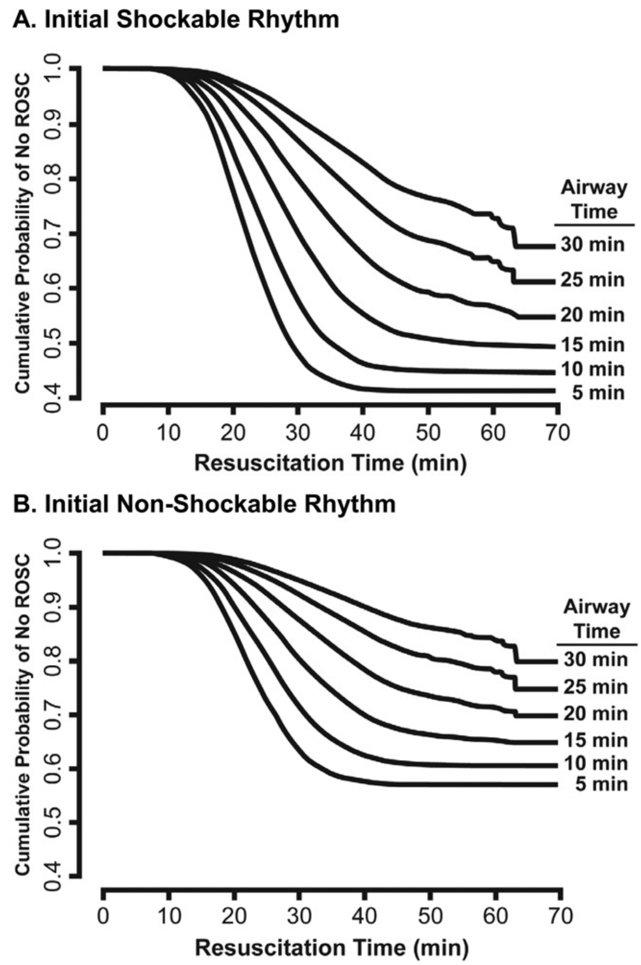

FIGURE 4. Theoretical survival curves. Theoretical survival curves estimated from the model are shown for illustrative purposes only and do not represent groups for statistical comparison. Resuscitation time (x-axis) begins at the arrival of Emergency Medical Services (EMS). The outcome is prehospital return of spontaneous circulation (ROSC), so a rapid drop on the y-axis indicates good patient outcomes. Separate analyses were conducted based on initial cardiac rhythm. Shockable: Ventricular tachycardia or ventricular fibrillation; Non-Shockable: Pulseless electrical activity, asystole, or no shock from EMS automated external defibrillator.

placement times were pushed back by multiple attempts, the majority of our cohort had only a single airway attempt. Given the negative time-dependent association is consistent throughout the resuscitation, the overall result is that early is better, even if select patients received multiple or prolonged attempts. However, it is possible that patients who specifically required multiple or prolonged attempts have a different probability of ROSC. The PRIMED Trial did not collect data on the timing of epinephrine administration; as a result, we could not test for an interaction between this and our exposure variable. Finally, given this is observational data, we can only assess for association and not causation.

Conclusions

In summary, the timing of advanced airway placement by EMS impacts the probability of prehospital ROSC. In witnessed OHCA patients who receive an intra-arrest advanced airway, placement as early as possible is associated with increased probability of achieving ROSC regardless of initial cardiac rhythm.

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