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Resuscitation

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Clinical paper

Fewer tracheal intubation attempts are associated with improved neurologically intact survival following out-of-hospital cardiac arrest



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Abstract

Background: International guidelines emphasize advanced airway management during out-of-hospital cardiac arrest (OHCA). We hypothesized that increasing endotracheal intubation attempts during OHCA were associated with a lower likelihood of favorable neurologic survival at discharge.

Methods: This retrospective, observational cohort evaluated the relationship between number of intubation attempts and favorable neurologic survival among non-traumatic OHCA patients receiving cardiopulmonary resuscitation (CPR) from January 1, 2015–June 30, 2019 in a large urban emergency medical services (EMS) system. Favorable neurologic status at hospital discharge was defined as a Cerebral Performance Category score of 1 or 2. Multivariable logistic regression, adjusted for age, sex, witness status, bystander CPR, initial rhythm, and time of EMS arrival, was performed using the number of attempts as a continuous variable.

Results: Over 54 months, 1205 patients were included. Intubation attempts per case were 1 = 757(63%), 2 = 279(23%), 3 = 116(10%), $\geq 4 = 49$ (4%), and missing/unknown in 4(<1%). The mean (SD) time interval from paramedic arrival to intubation increased with the number of attempts: 1 = 4.9(2.4) min, 2 = 8.0(2.9) min, 3 = 10.9(3.3) min, and $\geq 4 = 15.5(4.4)$ min. Final advanced airway techniques employed were endotracheal intubation (97%), supraglottic devices (3%), and cricothyrotomy (<1%). Favorable neurologic outcome declined with each additional attempt: 11% with 1 attempt, 4% with 2 attempts, 3% with 3 attempts, and 2% with 4 or more attempts (AOR = 0.41, 95% CI 0.25–0.68).

Conclusions: Increasing number of intubation attempts during OHCA resuscitation was associated with lower likelihood of favorable neurologic outcome.

Keywords: Emergency medical services, Heart arrest, Intubation, Intratracheal, Emergency medical technicians, Cardiopulmonary resuscitation, Airway management

Introduction

Resuscitation guidelines incorporate the use of advanced airway management to treat out-of-hospital cardiac arrest (OHCA).^{1–3} The optimal strategy for advanced airway management is not well-

defined, in part because the mechanisms of benefit and risk are not well understood.⁴ Advanced airways facilitate guideline-directed cardiopulmonary resuscitation (CPR) by enabling continuous chest compressions,⁵ a CPR best practice that is associated with greater odds of survival.⁶ However, placement of an advanced airway may interrupt chest compressions and adversely affect oxygenation and

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<https://doi.org/10.1016/j.resuscitation.2021.07.001>

Received 25 February 2021; Received in Revised form 23 June 2021; Accepted 3 July 2021

0300-9572/© 2021 Published by Elsevier B.V.

circulation^{7–11} without a clear survival advantage over non-invasive ventilatory strategies.^{12,13} As a consequence, some emergency medical services (EMS) agencies have transitioned away from endotracheal intubation to supraglottic airways during the treatment of patients in OHCA. Endotracheal intubation—the conventional advanced airway—also remains a standard because it achieves a higher order of airway protection and assures directed ventilation and oxygenation.

A key to optimizing the balance of risk and benefit is to understand how the process of intubation influences resuscitation outcome. In non-arrest circumstances, the need for multiple intubation attempts is associated with several adverse outcomes including hypoxia, esophageal intubation, aspiration, and dysrhythmia.¹⁴ However, the relationship between the number of intubation attempts and patient-centered clinical outcomes following OHCA has not yet been elucidated.^{15–18} This investigation explored whether the number of laryngoscopic attempts to place an endotracheal tube was associated with clinical outcomes following OHCA. We hypothesized that increasing intubation attempts would be associated with a lower likelihood of survival to discharge with favorable neurological status.

Methods

Study design, population, and setting

This retrospective, observational cohort study evaluated patients treated by the Seattle Fire Department for non-traumatic OHCA who received one or more laryngoscopic attempts as part of their resuscitative care from January 1, 2015 through June 30, 2019. The study *a priori* excluded patients who were not in cardiac arrest upon EMS arrival, had the initial attempt at intubation after first return of spontaneous circulation (ROSC), never received a laryngoscopic attempt, had a do not resuscitate (DNR) order, or received advanced life support (ALS) treatment from an outside agency prior to Seattle Fire Department involvement. The study was approved by the University of Washington Institutional Review Board and adhered to the STROBE guidelines for reporting on observational studies.¹⁹

The Seattle Fire Department is the primary provider of 9-1-1 EMS response in the City of Seattle, operating in a tiered response model.²⁰ The first tier is provided by firefighter-emergency medical technicians (EMTs), trained in CPR and basic life support (BLS). Equipped with automated external defibrillators (AEDs), EMTs arrive at the patient's side an average of 7 minutes after the 9-1-1 call is answered. The second-tier paramedics arrive at the patient's side an average of 4 minutes after the first tier and are trained in advanced life support (ALS), including electrocardiogram rhythm interpretation, manual defibrillation, insertion of intravenous and intraosseous catheters, administration of medications, and placement of advanced airway devices.

Paramedics employ direct laryngoscopy for endotracheal intubation as the primary advanced airway, following a standard airway management algorithm. Video laryngoscopy was not used during this study. Additional airway adjuncts include the iGel supraglottic airway device (Intersurgical, Berkshire, UK), cricothyroidotomy, and bougie stylet. In OHCA resuscitation, paramedics prioritize intubation and intravenous line placement upon arrival while the first-tier BLS personnel provide chest compressions and rescue breathing. Paramedics are trained to confirm endotracheal tube placement using waveform capnography immediately upon completion of intubation.

Successful endotracheal tube placement as documented by paramedics has been previously validated.²¹

Data variables and collection

We reviewed individual case records and organizational registries of advanced airway management and OHCA care to identify study variables. The OHCA registry uses dispatch, EMS, defibrillator, and hospital records to ascertain information about patient demographics, arrest circumstances, layperson care, as well as EMS and hospital therapies. The data was organized according to the Utstein template.²² The defibrillators recorded real-time audio, continuous waveforms of the electrocardiogram, end-tidal capnography (ETCO₂), peripheral arterial oxygen saturation, and transthoracic impedance. Following any attempted endotracheal intubation or advanced airway procedure, the paramedic who managed the airway completed a web-based Research Electronic Data Capture (REDCap) airway registry form.²³ The form includes patient characteristics, method and outcome for each placement attempt, the use of adjunctive medications, and details related to the procedure process.²⁴ Trained data abstractors then compared the airway survey to the time synchronized audio defibrillator recordings and adjudicated any differences.

Definitions

An endotracheal intubation attempt was defined as the introduction of a laryngoscope past the teeth and concluded when the laryngoscope was removed from the mouth, regardless of whether or not an endotracheal tube was inserted. We defined an attempt as successful if the endotracheal tube placement was confirmed by capnography.²¹ The 9-1-1 call time was used as a surrogate for the time of arrest, and the EMS arrival time was the first responding unit's arrival time at the patient's side and was approximated by the initial defibrillator turn-on time. The clocks in all defibrillators in the system are automatically synchronized to the atomic clock time at the time of transmission of the recording using the CodeStat software (Stryker Physio-Control, Redmond, WA). The time of endotracheal tube placement, or other final airway device, was defined as the time of the first ventilation via the advanced airway and was determined by audio recording of provider verbalization or by production of a capnography waveform by in-line ETCO₂.

Outcomes

The primary outcome was favorable neurologic status at hospital discharge, defined as a Cerebral Performance Category (CPC) score of 1 (mild or no neurological deficit) or 2 (moderate cerebral disability), consistent with current Utstein guidelines.²² Secondary outcomes were ROSC, survival to hospital admission, and survival to hospital discharge.

Analysis

We stratified patient, circumstance, care and outcome characteristics according to the number of intubation attempts. We used multivariable logistic regression to evaluate the association between outcome and the number of laryngoscopic attempts, using the number of attempts as a continuous variable. In the multivariable model, the odds ratio associated with number of attempts was adjusted for age, sex, witness status, bystander CPR, initial rhythm, and time interval from 9-1-1 call to ALS arrival. We *a priori* planned a separate analysis by presenting rhythm to discern the association between the number of intubation attempts and outcome according to rhythm (ventricular fibrillation [VF] or non-VF). Standard errors of regression

coefficients were adjusted for clustering of patients within paramedics. Analyses were performed using Stata/MP 16.1 (Statacorp, College Station, TX).

Results

Characteristics of study subjects

Of the 2093 patients treated for OHCA during the study period, 1205 patients were eligible for inclusion (Fig. 1). The most common reasons for exclusion were specified a-priori and comprised patients that did not receive ALS care ($n = 287$), arrested after EMS arrival ($n = 284$), or had the initial attempt at intubation after first ROSC ($n = 217$). Median age was 62 years and 68% of the patients were male (Table 1). Overall, 33% were bystander witnessed and 61% received bystander CPR. Initial shockable rhythm was present in 21% of cases. The mean (SD) time to successful placement of an advanced airway was 6.5 (3.7) minutes after ALS arrival at the patient's side.

Approximately two-thirds (63%) of patients were successfully intubated on the first attempt and 86% by the second attempt. Final advanced airway techniques employed at completion of EMS care were endotracheal intubation (97%), supraglottic devices (3%), and cricothyrotomy (<1%). Male patients were more likely to have additional intubation attempts than female patients. Patient age and bystander CPR did not differ as intubation attempts increased. The mean (SD) interval from ALS arrival to final advanced airway placement increased with the number of intubation attempts: 1 = 4.9(2.4) min, 2 = 8.0(2.9) min, 3 = 10.9(3.3) min, and $\geq 4 = 15.5(4.4)$ min. Stratified by number of intubation attempts, outcomes were depicted

with reference time to endotracheal intubation after ALS arrival (Fig. 2).

Main results

Overall, ROSC was achieved in 44% of cases, survival to hospital admission in 38%, survival to hospital discharge in 11%, and favorable neurological status at discharge in 8%. The proportion of patients with a favorable neurological status at discharge was 11% with the first attempt, 4% with the second attempt, 3% with the third attempt, and 2% with 4 or more attempts. In a multivariable adjusted model, the relative likelihood of favorable neurologic status at discharge decreased by 59% for every subsequent intubation attempt (adjusted odds ratio [AOR = 0.41, 95% CI 0.25–0.68]). Results were similar for secondary outcomes (Table 2). Survival to hospital discharge (AOR = 0.51, 95% CI 0.36–0.72), survival to hospital admission (AOR = 0.67, 95% CI 0.58–0.78), and ROSC (AOR = 0.66, 95% CI 0.57–0.75) declined as the number of intubation attempts increased (Table 3). In a subgroup analysis stratified by initial rhythm as either VF or not-VF, the association of increasing intubation attempts and worse outcomes persisted (Table 4).

Discussion

Among patients treated for OHCA using direct laryngoscopy to secure an endotracheal tube, we observed that an increasing number of intubation attempts was independently associated with lower odds of survival to discharge with favorable neurologic status. We observed a dose-dependent, inverse relationship between the number of intubation attempts and outcome whereby increasing intubation attempts was associated with a lower likelihood of favorable neurological survival. Secondary outcomes of ROSC, hospital admission, and survival to hospital discharge had similar relationships favoring fewer attempts.

Collectively, the results suggest the possibility that increasing attempts are more than a general confounding marker for a difficult resuscitation due to patient characteristics, patient location, or teamwork challenges. Additional intubation attempts may lead to additional periods of apnea that may mechanically contribute to lower likelihood of favorable neurologic status at hospital discharge.

We observed that increasing attempts were associated with longer intervals from ALS arrival to successful intubation. Although patients with increasing attempts were more likely to be male, this difference was incorporated and adjusted in the multivariable model. Other process measures of advanced care did not differ according to the number of intubation attempts.

There is a complex relationship between time-dependent variables, such as intubation attempts, that interact with outcomes. Assessing outcomes in relation to airway management is confounded by receipt and response to interventions early in the course of resuscitation, such as successful defibrillation with restoration of consciousness that precludes the need for an advanced airway. Similarly, in the case of a failed airway management attempt(s), a patient must “survive” long enough to have subsequent attempts at intubation.²⁵ Prior to the current study, multiple attempts at intubation undeniably confer a delay in securing an advanced airway, yet the number of attempts was of unclear clinical significance. While previous studies evaluating the time to airway placement report conflicting findings,^{26–28} a large North American prehospital database found

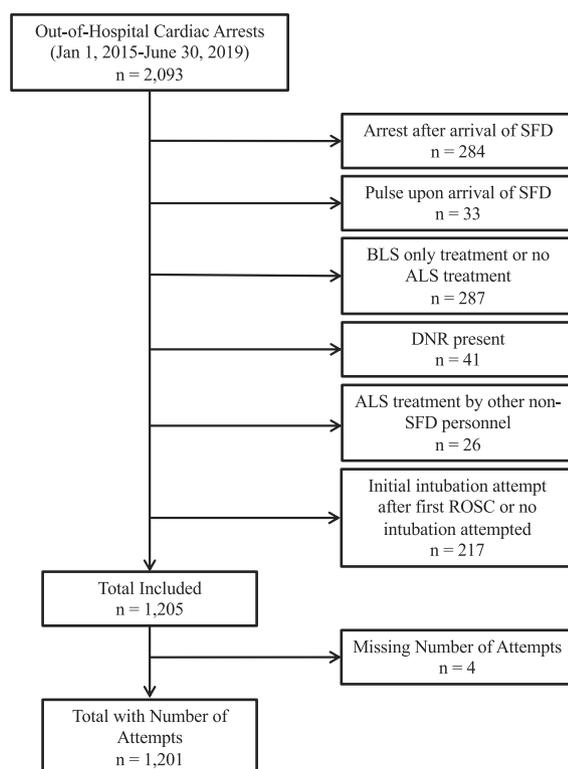


Fig. 1 – Flow diagram.

Table 1 – Demographics and characteristics of clinical care of patients who experienced out-of-hospital cardiac arrest (OHCA), stratified by number of intubation attempts (n = 1205). Cardiopulmonary resuscitation (CPR); automated external defibrillator (AED); advanced life support (ALS).

Characteristics	Overall (n = 1205)	Number of Intubation Attempts			
		1 (n = 757)	2 (n = 279)	3 (n = 116)	4+ (n = 49)
Age, mean (SD)	61.5 (33.0)	61.9 (39.0)	60.6 (19.2)	61.7 (20.5)	58.8 (17.8)
Age < 16 (%)	18 (1.5%)	8 (1.1%)	6 (2.2%)	3 (2.6%)	1 (2.0%)
Male sex, n (%)	814 (67.6%)	493 (65.1%)	195 (69.9%)	83 (71.6%)	43 (87.8%)
Location of Arrest					
Home/Other residence (%)	752 (62.4%)	460 (60.8%)	176 (63.1%)	83 (71.6%)	29 (59.2%)
Healthcare facility (%)	124 (10.3%)	83 (11.0%)	29 (10.4%)	7 (6.0%)	5 (10.2%)
Public (%)	316 (26.2%)	208 (27.4%)	71 (25.4%)	24 (20.7%)	13 (26.5%)
Other (%)	13 (1.1%)	6 (0.8%)	1 (0.4%)	2 (1.7%)	2 (4.1%)
OHCA etiology (Utstein)					
Medical (%) - presumed cardiac or other medical etiologies	1,043 (86.6%)	648 (85.6%)	240 (86.0%)	105 (90.5%)	46 (93.9%)
Drug Overdose (%)	111 (9.2%)	78 (10.3%)	25 (9.0%)	6 (5.2%)	2 (4.1%)
Drowning: Without an alternative causation (%)	11 (0.9%)	7 (0.9%)	3 (1.1%)	1 (0.9%)	0 (0.0%)
Asphyxial (%)	31 (2.6%)	18 (2.4%)	10 (3.6%)	2 (1.7%)	1 (2.0%)
Other (%)	6 (0.5%)	3 (0.4%)	1 (0.4%)	2 (1.7%)	0 (0.0%)
Unknown (%)	3 (0.3%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Witness status					
Witnessed	398 (33.0%)	253 (33.4%)	100 (35.8%)	34 (29.3%)	11 (22.5%)
Unwitnessed	795 (66.0%)	495 (65.4%)	176 (63.1%)	82 (70.7%)	38 (77.6%)
Unknown	12 (1.0%)	9 (1.2%)	3 (1.1%)	0 (0.0%)	0 (0.0%)
Bystander CPR performed, n (%)	733 (60.8%)	464 (61.3%)	174 (62.4%)	64 (55.2%)	29 (59.2%)
Use of public access AED, n (%)	50 (4.2%)	36 (4.8%)	7 (2.5%)	3 (2.6%)	4 (8.2%)
Shock delivered by public access AED, n (%)	10 (7.6%)	8 (8.8%)	0 (0.0%)	0 (0.0%)	2 (4.1%)
Initial arrest rhythm					
PEA/Asystole, n (%)	913 (75.8%)	568 (75.0%)	216 (77.4%)	88 (75.9%)	38 (77.6%)
VF/VT, n (%)	257 (21.3%)	167 (22.1%)	56 (20.1%)	24 (20.7%)	9 (18.4%)
Unknown, but not shocked by public access or BLS AED, n (%)	27 (2.2%)	16 (2.1%)	6 (2.2%)	3 (2.6%)	2 (4.1%)
Unknown, without use of public access of BLS AED, n (%)	8 (0.7%)	6 (0.8%)	1 (0.4%)	1 (0.9%)	0 (0.0%)
Defibrillation use, n (%)	441 (26.6%)	276 (36.4%)	107 (38.4%)	40 (34.5%)	17 (34.7%)
Epinephrine use, n (%)	1176 (99.2%)	732 (98.8%)	276 (99.0%)	115 (99.1%)	49 (100%)
Antiarrhythmic use, n (%)	236 (19.9%)	152 (20.5%)	50 (18.1%)	26 (22.6%)	8 (16.3%)
9–1–1 call to first Epinephrine, mean minutes (SD)	16.6 (5.3)	16.5 (5.2)	16.7 (4.8)	16.9 (6.6)	17.1 (5.6)
ALS arrival to first Epinephrine, mean minutes (SD)	6.3 (3.1)	6.2 (2.8)	6.6 (3.5)	6.5 (4.0)	6.6 (2.7)

Table 1 – (continued)

Characteristics	Number of Intubation Attempts				
	Overall (n = 1205)	1 (n = 757)	2 (n = 279)	3 (n = 116)	4+ (n = 49)
Advanced airway device employed					
Endotracheal tube, n (%)	1167 (96.8%)	750 (99.1%)	276 (99.0%)	102 (87.9%)	35 (71.4%)
Supraglottic device, n (%)	34 (2.8%)	5 (0.7%)	2 (0.7%)	13 (11.2%)	14 (28.6%)
Cricothyrotomy, n (%)	3 (0.3%)	1 (0.1%)	1 (0.4%)	1 (0.9%)	0 (0.0%)
Bag-Valve Mask, n (%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
9–1-1 call to final advanced airway device employed, mean minutes (SD)	16.8 (5.6)	15.3 (5.0)	18.1 (4.2)	21.4 (6.3)	26.4 (5.8)
ALS arrival at patient to final advanced airway device employed, mean minutes (SD)	6.5 (3.7)	4.9 (2.4)	8.0 (2.9)	10.9 (3.3)	15.5 (4.4)

*n = 4 unknown number of attempts.

lower rates of survival for every additional minute needed to place an advanced airway regardless of the presenting rhythm.²⁹ Our finding of a dose-dependent relationship between increasing intubation attempts and lower likelihood of favorable neurologic status at hospital discharge offers pragmatic insight that may inform airway processes. Considering the various critical and time-sensitive actions prioritized during resuscitation from cardiac arrest, measures that promote first pass success without interrupting CPR and thus limit the number of intubation attempts may offer survival benefit.

In this study, we report a first pass endotracheal intubation success rate of 65%. While this study excluded patients who had achieved ROSC at time of first intubation attempts, as they were thought to represent a distinct patient group with more favorable intubating conditions and prognosis, prior work from this EMS system has reported similar first pass success (72%) for intra-arrest laryngoscopic attempts in King County.²¹ We speculate that the level of success may be related to challenges imposed by ongoing chest compressions, position of patients on the floor, and limited ability to perform pre-procedure head positioning optimization. A modestly higher first pass success rate (70%) with direct laryngoscopy for emergency department patients in cardiac arrest was reported from Japan in 2018.³⁰

The results of the current study in conjunction with prior investigation supports training and clinical care strategies to achieve first attempt intubation success during OHCA resuscitation. An example of an intervention that could be implemented to increase first pass success is routine use of the gum elastic bougie. In our EMS system, the introduction of routine use of the bougie stylet with first attempt at laryngoscopy increased first pass success by 9% among patients in cardiac arrest.³¹ Adoption of measures that may prevent multiple or prolonged attempts at laryngoscopy should be considered as a means to mitigate interruptions in gas exchange, avoid interruptions in chest compressions,³² and the resultant diminished coronary perfusion pressures thought to worsen myocardial and neurologic injuries. Similarly, implementation of protocolized strategy of transitioning to a supraglottic device after prespecified number of intubation attempts may be considered to limit the cumulative apneic time during the resuscitation.³³

This study has limitations. We appreciate that the results of this study are derived from retrospective data thus limiting any causal inference. This study is from a single, large urban EMS system that employs endotracheal intubation as primary means of airway management during resuscitation of OHCA, such that the results may have limited generalizability for systems that use supraglottic airway as the initial advanced airway strategy or specifically delay advanced airway therapy until ROSC or some other designated clinical (time) point. Nonetheless, the current investigation harnesses audio and monitor downloads to accurately describe the granularity of time-specific interventions, making this assessment unique in the literature on the topic of the airway interventions after OHCA. This study uses registries populated without specific knowledge of the current study aims, though the observational design does not enable a definitive assessment of causality. While the airway registry information is self-reported by the treating paramedics and therefore subject to recall bias, the data entered was compared to the audio defibrillator recording by trained data abstractors who adjudicated any observed differences. Despite this granular review, we are unable to report the number of patients who were not intubated successfully on the first attempt, then developed a pulse, and then were intubated on a subsequent attempt. We also acknowledge the possibility that

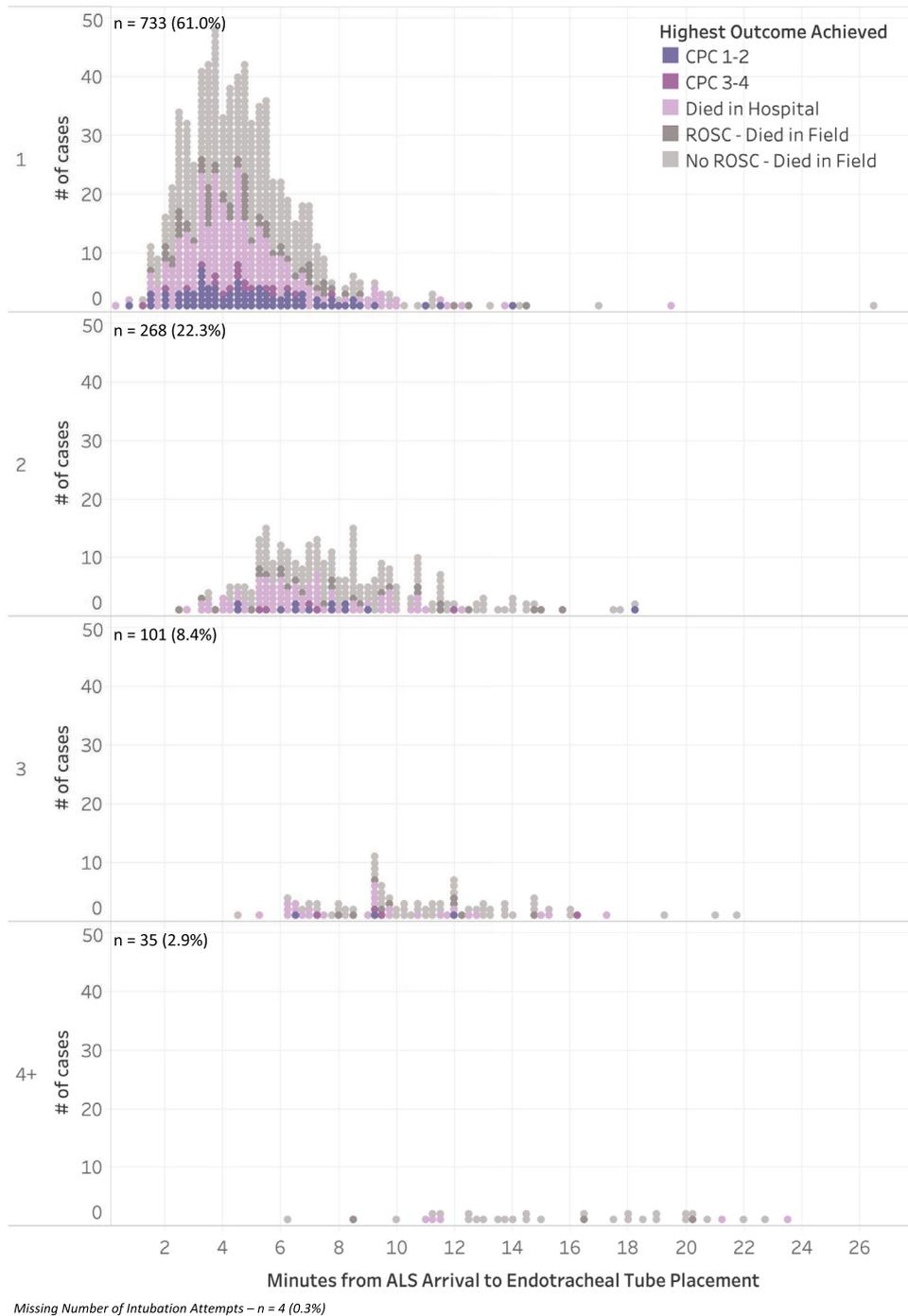


Fig. 2 – Outcome of OHCA by number of intubation attempts and time to endotracheal intubation after ALS arrival. Seattle Fire Department (SFD); Basic Life Support (BLS); Do Not Resuscitate (DNR); Advanced Life Support (ALS); Return of Spontaneous Circulation (ROSC); Out-of-Hospital Cardiac Arrest (OHCA).

an unmeasured confounder such as cumulative dose of epinephrine administered or simply passage of time in a low flow state could account for some or all of the differences observed. Ultimately, these

limitations should be considered in the context of the study’s strengths of a relatively large sample size, detailed reporting of airway events, and the granular timing of resuscitative care.

Table 2 – Clinical outcomes of patients who had an out-of-hospital cardiac arrest (OHCA), stratified by number of intubation attempts (n = 1205). Return of spontaneous circulation (ROSC).

Outcomes	Overall (n = 1,205)	Number of Intubation Attempts			
		1 (n = 757)	2 (n = 279)	3 (n = 116)	4+ (n = 49)
ROSC, n (%)	526 (43.7%)	363 (48.0%)	117 (42.0%)	39 (33.6%)	7 (14.3%)
Survival to hospital admission, n (%)	452 (37.5%)	316 (41.7%)	95 (34.1%)	33 (28.4%)	7 (14.3%)
Survival to hospital discharge, n (%)	127 (10.5%)	102 (13.5%)	17 (6.1%)	7 (6.0%)	1 (2.0%)
Cerebral Performance Category 1–2, n (%)	98 (8.1%)	82 (10.8%)	12 (4.3%)	3 (2.6%)	1 (2.0%)

n = 4 unknown number of attempts.

Table 3 – Association between number of intubation attempts and clinical outcomes, reported as odds ratios and 95% confidence intervals: results from logistic regression.

Outcome	Unadjusted (n = 1181)	Adjusted (n = 1165)
ROSC	0.67 (0.59–0.76)	0.66 (0.57–0.75)
Admission to the hospital	0.69 (0.60–0.80)	0.67 (0.58–0.78)
Discharged alive	0.53 (0.39–0.74)	0.51 (0.36–0.72)
Good neurologic function	0.45 (0.28–0.70)	0.41 (0.25–0.68)

Adjusted for age, sex, witness status, bystander CPR, VF as initial rhythm, and interval from 9-1-1 call to ALS arrival. Cardiopulmonary resuscitation (CPR); ventricular fibrillation (VF); advanced life support (ALS).

Table 4 – Association between number of intubation attempts and clinical outcomes stratified by initial electrocardiogram rhythm as ventricular fibrillation (VF) or not-VF, reported as adjusted odds ratios and 95% confidence intervals: results from logistic regression.

Outcome	VF (n = 252)	Not VF (n = 913)
ROSC	0.68 (0.49–0.95)	0.65 (0.54–0.77)
Admission to the hospital	0.76 (0.57–1.00)	0.64 (0.53–0.79)
Discharged alive	0.54 (0.36–0.81)	0.43 (0.21–0.92)
Good neurologic function	0.55 (0.36–0.81)	*

Adjusted for age, sex, witness status, bystander CPR, and interval from 9-1-1 call to ALS arrival. In all cases increasing numbers of intubation attempts were associated with worse outcomes. For example, in the VF group, the odds of being discharged alive decreased 43% for each additional intubation attempt. Cardiopulmonary resuscitation (CPR); ventricular fibrillation (VF); advanced life support (ALS).

*Unstable model as the number of attempts perfectly predicts good neurologic function (21 subjects with good neurologic function, all 21 had a single intubation attempt).

Conclusions

Increasing number of intubation attempts during OHCA resuscitation was associated with lower likelihood of favorable neurologic outcome. As EMS stakeholders consider the role of endotracheal intubation in resuscitation, attention should be directed to the number of intubation attempts, the potential clinical consequences of repeated attempts, and strategies to promote proficiency.

CRedit authorship contribution statement

All authors have made substantial contributions to the conception of the study, or acquisition of data, or analysis and interpretation of data; Contributed to the drafting the article and/or critical revisions; And have given final approval of the submitted version. The authors have no additional writing assistance to disclose.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We wish to acknowledge the dedicated efforts of the telecommunicators and EMS professionals of the Seattle Fire Department and their sustained efforts at improving the resuscitative care delivered to the community they serve. This project was partially funded by a research grant from the Medic One Foundation.

The submitted manuscript and abstract complies with word count parameters for an original paper.

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