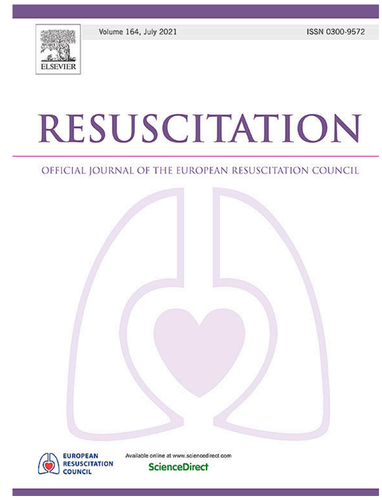
Journal Pre-proofs



Clinical paper

Supraglottic Airway Devices are Associated with Asphyxial Physiology After Prolonged CPR in Patients with Refractory Out-of-Hospital Cardiac Arrest Presenting for Extracorporeal Cardiopulmonary Resuscitation

Jason A. Bartos, Arianne Clare Agdamag, Rajat Kalra, Lindsay Nutting, R.J. Frascone, Aaron Burnett, Nik Vuljaj, Charles Lick, Peter Tanghe, Ryan Quinn, Nicholas Simpson, Bjorn Peterson, Kari Haley, Kevin Sipprell, Demetris Yannopoulos

PII: S0300-9572(23)00082-5
DOI: https://doi.org/10.1016/j.resuscitation.2023.109769
Reference: RESUS 109769

To appear in: *Resuscitation*

Received Date: 3 January 2023
Revised Date: 8 March 2023
Accepted Date: 9 March 2023

Please cite this article as: J.A. Bartos, A. Clare Agdamag, R. Kalra, L. Nutting, R.J. Frascone, A. Burnett, N. Vuljaj, C. Lick, P. Tanghe, R. Quinn, N. Simpson, B. Peterson, K. Haley, K. Sipprell, D. Yannopoulos, Supraglottic Airway Devices are Associated with Asphyxial Physiology After Prolonged CPR in Patients with Refractory Out-of-Hospital Cardiac Arrest Presenting for Extracorporeal Cardiopulmonary Resuscitation, *Resuscitation* (2023), doi: https://doi.org/10.1016/j.resuscitation.2023.109769

Manuscript submitted to the Resuscitation

Supraglottic Airway Devices are Associated with Asphyxial Physiology After Prolonged CPR in Patients with Refractory Out-of-Hospital Cardiac Arrest Presenting for Extracorporeal Cardiopulmonary Resuscitation

Jason A. Bartos MD, PhD,[1,2] Arianne Clare Agdamag MD,[1] Rajat Kalra MBChB, MS,[1] Lindsay Nutting DNP,[1] R.J. Frascone MD,[3] Aaron Burnett MD,[4] Nik Vuljaj MD,[5] Charles Lick MD,[6] Peter Tanghe MD,[7] Ryan Quinn,[8] Nicholas Simpson MD,[9] Bjorn Peterson MD,[3] Kari Haley MD,[3] Kevin Sipprell MD,[10] Demetris Yannopoulos MD[1,2]

[1]Division of Cardiology, Department of Medicine, University of Minnesota School of Medicine, Minneapolis, Minnesota
[2]Center for Resuscitation Medicine, University of Minnesota School of Medicine, Minneapolis, Minnesota
[3]Department of Emergency Medicine, Regions Hospital, St. Paul, Minnesota
[4]Woodbury and Cottage Grove, Emergency Medical Services, Minnesota
[5]M Health Fairview Emergency Medical Services, Minneapolis, Minnesota
[6]Allina Health Emergency Medical Services, Minneapolis, Minnesota
[7]Department of Emergency Medicine, North Memorial Health Ambulance Service, North Memorial Health Medical Center, Robbinsdale, MN
[8]Edina Fire Department, Edina, Minnesota
[9]Hennepin Emergency Medical Services, Minneapolis, Minnesota
[10]Department of Emergency Medicine, Ridgeview Medical Center, Waconia, Minnesota

Short Title: Airway Effects in Refractory Cardiac Arrest

Total word count: 3077
Abstract word count: 247
Tables and Figures: 3 figs, 2 tables

Corresponding Author:

Jason Bartos
UMN – Cardiology Division
420 Delaware Street SE
MMC 508
Minneapolis, MN 55455
Telephone: 612-625-9764
Fax: 612-626-4411.
E-mail: jabartos@umn.edu
Twitter: @jason_bartos

Abstract

Background: Multiple randomized clinical trials have compared specific airway management strategies during ACLS with conflicting results. However, patients with refractory cardiac arrest died in almost all cases without the availability of extracorporeal cardiopulmonary resuscitation (ECPR). Our aim was to determine if endotracheal intubation (ETI) was associated with improved outcomes compared to supraglottic airways (SGA) in patients with refractory cardiac arrest presenting for ECPR.

Methods: We retrospectively studied 420 consecutive adult patients with refractory out-of-hospital cardiac arrest due to shockable presenting rhythms presenting to the University of Minnesota ECPR program. We compared outcomes between patients receiving ETI (n=179) and SGA (n=204). The primary outcome was the pre-cannulation arterial PaO_2 upon arrival to the ECMO cannulation center. Secondary outcomes included neurologically favorable survival to hospital discharge and eligibility for VA-ECMO based upon resuscitation continuation criteria applied upon arrival to the ECMO cannulation center.

Results: Patients receiving ETI had significantly higher median PaO_2 (71 vs. 58 mmHg, p=0.001), lower median $PaCO_2$ (55 vs. 75 mmHg, p<0.001), and higher median pH (7.03 vs. 6.93, p<0.001) compared to those receiving SGA. Patients receiving ETI were also significantly more likely to meet VA-ECMO eligibility criteria (85% vs. 74%, p=0.008). Of patients eligible for VA-ECMO, patients receiving ETI had significantly higher neurologically favorable survival compared to SGA (42% vs. 29%, p=0.02).

Conclusions: ETI was associated with improved oxygenation and ventilation after prolonged CPR. This resulted in increased rate of candidacy for ECPR and increased neurologically favorable survival to discharge with ETI compared to SGA.

Keywords: Refractory cardiac arrest, cardiac arrest, ventricular fibrillation, extracorporeal cardiopulmonary resuscitation, endotracheal intubation, supraglottic airway, out-of- hospital cardiac arrest

Introduction:

Airway management remains a critical component of advanced cardiac life support (ACLS) in patients suffering from out-of-hospital cardiac arrest (OHCA).[1, 2] Strategies vary between communities and emergency medical services (EMS) ranging from use of bag valve mask (BVM) to supraglottic airways (SGA) to endotracheal intubation (ETI). Randomized trials comparing these airway strategies demonstrated mixed results with most finding no significant differences.[3-5] Consequently, guidelines suggest that any airway strategy is acceptable with appropriate consideration of the expertise of available providers.[1]

Importantly, the clinical trials relied on standard ACLS which results in two distinct patient populations: 1) patients with return of spontaneous circulation (ROSC) prior to hospital arrival, most likely occurring after short durations of cardiopulmonary resuscitation (CPR),[6-9] and 2) patients with refractory cardiac arrest and failure to achieve ROSC resulting in death. In recent years, extracorporeal cardiopulmonary resuscitation (ECPR) has been shown to improve survival for patients with refractory cardiac arrest.[10-14] Patients receiving ECPR commonly receive prolonged CPR (≥60 minutes) before initiation of flow from the extracorporeal membrane oxygenation (ECMO) circuit. Prior studies have demonstrated worsening metabolic derangement and reduced likelihood of ROSC and survival during prolonged CPR, but the potential for specific ACLS strategies to improve pathology remains unknown.[6, 8, 9, 12]

This study aimed to compare the pathophysiologic effects of ETI or SGA as the primary airway management strategies for patients with refractory cardiac arrest and shockable presenting rhythms presenting for ECPR. Specifically, the impact of airway strategy on metabolic derangement and survival to discharge were assessed.

Methods

Study Design and Study Population

Consecutive patients treated with the University of Minnesota refractory out-of-hospital ventricular fibrillation/ventricular tachycardia (VF/VT) ECPR (UMN-ECPR) protocol between December 1, 2015 and September 3, 2022 were included in this study. For the purposes of this investigation, only patients that received endotracheal intubation or supraglottic airways were included in the study cohort. The Institutional Review Board at the University of Minnesota approved this study (No. 1703M11301) with waiver of informed consent.

Details of the UMN-ECPR protocol were published previously.[10, 15-17] Briefly, patients with refractory VF/VT OHCA were rapidly transported to an ECMO cannulation hospital for immediate initiation of mechanical circulatory support with peripheral veno-arterial (VA) ECMO, invasive coronary angiography with percutaneous coronary intervention as indicated, and admission to a specialized intensive care unit using a protocolized post-arrest care pathway.[18, 19] Prehospital patient screening was performed by paramedics with transport of patients meeting the following criteria: (1) 18-75 years of age, (2) initial rhythm of VF/VT, (3) ongoing cardiac arrest despite 3 direct current shocks or shock resulting in ongoing pulseless electrical activity or asystole, (4) received ≥300mg of amiodarone, (5) body habitus accommodating a Lund University Cardiac Arrest System (LUCAS®, Lund, Sweden), and (6) estimated transfer time to ECMO cannulation center of <30 min. Patients were excluded from this protocol if they were nursing home residents, were known to have do not resuscitate/do not intubate orders, have trauma as the cause of the cardiac arrest, or have known pre-arrest terminal illness. The study protocol did not specify the methods of airway management in the prehospital setting or the ventilation strategy. Patients were transported to the ECMO cannulation hospital with ongoing mechanical CPR and ACLS. Upon arrival, arterial blood gas (ABG) and lactic acid levels were immediately assessed. Patients failing to meet ≥1 of the following resuscitation continuation criteria were considered ineligible for VA-ECMO cannulation and declared dead on arrival: (1) end-tidal CO_2 ($ETCO_2$) ≥10 mmHg, (2) arterial partial pressure of oxygen (PaO_2) ≥50 mmHg, (3) arterial lactic acid ≤18 mmol/L.[15]

Patients meeting the resuscitation continuation criteria underwent immediate cannulation and initiation of peripheral VA-ECMO by interventional cardiologists with ultrasound and fluoroscopy guidance. Coronary angiography was performed, and percutaneous coronary intervention was provided as indicated. Additional anti-arrhythmic therapy was also provided as indicated. If an organized cardiac rhythm could not be established after 90 minutes of stabilized hemodynamics and treatment of reversible causes of the cardiac arrest, the patient was declared dead. Patients with an organized cardiac rhythm were admitted to the cardiac intensive care unit. Comprehensive post-arrest care was provided as described previously.[18]

Study Outcomes

Patients were divided into two groups based on the initial airway management strategy chosen by the paramedics: (1) endotracheal intubation, (2) supraglottic airways. An intention-to-treat type design was used with group designation determined by the first airway management strategy attempted. Supraglottic airways included the following: igel, LMA, and AirQ. The primary outcome was the pre-cannulation PaO_2 from the arterial blood gas taken at the time of arrival to the ECMO cannulation center. Secondary outcomes included the remaining arterial blood values upon arrival to the ECMO cannulation center, neurologically favorable survival to hospital discharge, and candidacy for VA-ECMO at the time of arrival to the ECMO cannulation center based on permissive resuscitation continuation criteria.

Two groups were defined for the purpose of evaluating neurologic outcome in patients receiving full resuscitation efforts: (1) favorable neurologic outcome, defined as cerebral performance category (CPC) 1-2 and (2) poor neurologic outcome, including patients who died or had significant neurologic impairment despite full resuscitation efforts (CPC 3-5). VA-ECMO-ineligible patients were defined as those excluded from receiving VA-ECMO due to failure of the resuscitation continuation criteria (PaO_2, arterial lactic acid, $ETCO_2$).

Data Collection and Statistical Analyses

All data were obtained by the study authors via chart review. Data were placed in a REDCap database hosted at the University of Minnesota. They were then exported to Excel for biostatistical analysis. Normally distributed continuous variables were summarized as means ± standard deviations with comparisons using t-test or analysis of variance. The Tukey HSD correction was used for pairwise comparisons. Non-normally distributed continuous variables were summarized as medians with interquartile ranges with comparisons using the Wilcoxon Rank-Sum and Kruskal-Wallis tests. Categorical variables were summarized as counts and proportions with comparisons using the chi-squared and Fisher's exact tests.

The association between poor neurologic outcomes and airway strategy was also assessed using multinomial logistic regression with two models. Model 1 adjusted for age, sex, and use of bystander CPR. Model 2 adjusted for age, sex, use of bystander CPR, and duration of professional CPR prior to initiation of VA-ECMO. All variables were chosen *a priori* due to their established associations with neurologic outcomes in OHCA. The association between ineligibility for VA-ECMO and airway strategy was also assessed using these two models. The results of the adjusted analyses were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). All hypothesis testing was two-tailed with level of significance set at 0.05 for all analyses. All analyses were performed in StataMP 15.1.

Results

Between December 1, 2015 and September 3, 2022, 420 patients with refractory VF/VT OHCA were transported to an ECMO cannulation center with ongoing CPR by ACLS-certified paramedics as part of the UMN-ECPR protocol (Figure 1). Of these, 179/420 (43%) patients received ETI and 204/420 (49%) received SGA as the initial airway management strategies. Other airways, including bag valve mask with oropharyngeal or nasopharyngeal airways, were used exclusively in 37/420 (9%) patients; these patients were excluded from the study. Therefore, 383 patients were included in this study with either ETI or SGA. Of those patients receiving ETI as the initial strategy, ETI was successful in 169/179 (94.4%) cases with 10 patients converted to SGA as a secondary strategy. No patients in the SGA group converted to ETI.

Baseline Characteristics

Patients were predominantly male (311/383 [81%]) and white (308/383 [80%]), with mean age 57±12 years (Table 1). Most arrests were witnessed (295/383 [77%]) with bystander CPR provided in 267/383 (70%). Professional CPR was delivered for 62±20 min prior to initiation of VA-ECMO. There were no statistically significant differences between groups.

Association Between Airway Management Strategy and Arterial Blood Results

The initial airway management strategy was significantly associated with arterial blood gas results at the time of evaluation for VA-ECMO cannulation upon arrival to the cannulation center (Table 2). ETI was associated with significantly higher PaO_2 compared to SGA (71 vs. 58 mmHg, p<0.001, Figure 2A). Importantly, $PaCO_2$ was significantly lower (55 vs. 75 mmHg, p<0.001, Figure 2B) while pH was significantly higher (7.03 vs. 6.93, p<0.001) in ETI patients. The lactic acid levels were not significantly different between the airway groups (11.8 vs. 12.0, p=0.35, Figure 2C).

Association Between Airway Management Strategy and Patient Outcomes

Overall, 302/383 (79%) patients were eligible for VA-ECMO cannulation upon arrival to the ECMO cannulation center based on the pre-specified resuscitation continuation criteria including $ETCO_2$ ≥10 mmHg, PaO_2 ≥50 mmHg, and arterial lactic acid ≤18 mmol/L (Table 2). Patients receiving ETI were significantly more likely than patients with SGAs to be eligible for VA-ECMO (152/179 [85%] vs. 150/204 [74%], p=0.008, Table 2 and Figure 3). Of those patients that failed the resuscitation continuation criteria, and were thereby ineligible for VA-ECMO cannulation, 76/81 (94%) failed due to PaO_2 <50 mmHg. Patients with ETI were significantly less likely to have PaO2 <50mmHg when compared to patients with SGAs (23/179 [13%] vs. 53/204 [26%], p=0.001). There was no significant difference between ETI and SGA patients in failure of the lactic acid criteria (5/179 [3%] vs. 15/204 [7%], p=0.06). Two patients failed the $ETCO_2$ criteria, one from each group, while both patients also failed the PaO_2 and lactic acid criteria.

Patients who failed the resuscitation continuation criteria with PaO_2<50 mmHg also exhibited other ABG anomalies at the time of arrival at the cannulation center. The median PaO_2 was 34.0 (22.3, 42.8) mmHg for this population while the $PaCO_2$ was 104.0 (85.0, 121.0) mmHg, the presenting pH was 6.80 (6.75, 6.91), and the presenting lactic acid was 15.0 (11.3, 18.0) mmol/L.

Of patients eligible for VA-ECMO, patients receiving ETI had significantly higher neurologically favorable survival compared to SGA (64/152 [42%] vs. 44/150 [29%], p=0.02, Table 2). Overall outcomes were also significantly different with increased neurologically favorable survival associated with ETI (64/179 [36%] vs. 44/204 [22%], p=0.04, Figure 3)

Adjusted Analyses of Airway Strategy and Neurological Outcomes

For patients eligible for VA-ECMO, use of SGA as the initial airway strategy was associated with an odds ratio of 1.67 (95% CI: 1.02-2.72) for poor neurologic outcome (CPC 3-5) compared to ETI after adjusting for age, sex, and occurrence of bystander CPR. Similarly, the odds ratio for CPC 3-5 was 1.73 (95% CI: 1.03-2.93) in patients that received SGA compared to ETI after adjusting for age, sex, occurrence of bystander CPR, and duration of professional resuscitation before VA-ECMO initiation.

In the overall study population, the odds of being ineligible for VA-ECMO were 2.80 (95% CI: 1.52-5.13) times higher among patients that received SGA rather than ETI after adjusting for age, sex, and occurrence of bystander CPR. Similarly, the odds of VA-ECMO ineligibility were 2.79 (95% CI: 1.47-5.27) times higher in patients that received SGA rather than ETI after adjusting for age, sex, occurrence of bystander CPR, and duration of professional resuscitation before VA-ECMO initiation.

Discussion

Successful treatment of refractory cardiac arrest requires prolonged periods of effective ACLS to sustain a survivable metabolic state until additional therapies can be deployed. Multiple studies of ECPR for refractory cardiac arrest have observed average durations of professional CPR of 60 minutes or more.[10-12, 20-23] However, patient outcomes with ECPR worsen substantially with longer CPR durations demonstrating that current ACLS methods are not sufficient to maintain survivable physiology in most patients. This study is the first, to our knowledge, to examine differences in ACLS techniques specifically in refractory cardiac arrest patients. The results demonstrate that use of ETI in this large refractory cardiac arrest cohort transported for ECPR was associated with improved oxygenation and ventilation upon patient arrival when compared to patients with SGAs. Further, the asphyxial physiology demonstrated in patients with SGAs significantly decreased eligibility for VA-ECMO leading to increased overall mortality in patients receiving SGAs. Importantly, for patients who met resuscitation continuation criteria and received VA-ECMO, ETI was associated with improved neurologically favorable survival compared to patients with SGAs.

Multiple non-randomized studies of cardiac arrest patients have compared airway management techniques with mixed results in general cardiac arrest populations. A secondary analysis of the Resuscitation Outcomes Consortium (ROC) PRIMED trial compared patients with successful ETI vs. successful SGA deployment.[24] This comparison demonstrated increased rates of ROSC and survival to hospital discharge in patients with ETI. Analysis of the Cardiac Arrest Registry to Enhance Survival (CARES) demonstrated similar results with improved ROSC rates and neurologically favorable survival with ETI compared to SGA.[25] Importantly, both of these studies had very low survival rates overall with 4.7% and 5.4%, respectively. A meta-analysis including 10 observational studies and over 75,000 patients concluded that ETI was associated with increased likelihood of ROSC and neurologically favorable survival.[26] However, a large study including nearly 650,000 patients from the All-Japan Utstein Registry demonstrated similar rates of neurologically favorable survival with ETI and SGA, but both were significantly lower than patients receiving BVM.[27]

Randomized clinical trials examining the effect of airway management also showed conflicting results when comparing airway management strategies in unselected patients with OHCA.[3-5] Benger et al.[4] randomized 9296 patients with OHCA to SGA vs. ETI in the AIRWAYS-2 trial demonstrating no significant difference between airway management strategies. Importantly, ECPR was not available for these patients with 55% of patients dying at the scene with refractory arrest and only 20% achieving hospital admission. Patients without prehospital ROSC had <1% survival in this study. Similarly, Wang et al.[5] randomized 3004 patients with OHCA to SGA vs. ETI but 40% died at the scene with refractory arrest. They found improved rates of prehospital ROSC, survival to hospital discharge, and neurologically favorable survival in patients receiving SGAs. Given that ECPR was not widely used in these trials, and multiple studies have shown a strong association between duration of CPR and likelihood of ROSC over the first 30 minutes of CPR,[6-9, 12] it should be remembered that most survivors in these studies had short durations of CPR and patients with refractory cardiac arrest largely died due to lack of ROSC. Therefore, while important for management of cardiac arrest overall, the lessons of these trials cannot be applied directly to treatment of refractory cardiac arrest where prolonged CPR and ECPR are performed.

Together with this study, these data suggest that ACLS may be considered in two phases, early ACLS and refractory ACLS, with different strategies to optimize oxygenation and ventilation in each phase. Early ACLS, likely including the first 15-30 minutes of ACLS, requires rapid stabilization and maintenance of a near-normal physiologic state to maximize opportunities for ROSC. This includes high quality CPR, defibrillation as indicated, expeditious airway management based on EMS expertise, and likely vascular access and medication delivery. Resource limitations may favor simplified and rapidly deployable tools as seen in the Benger and Wang trials. Most clinical trials investigating ACLS therapies are pertinent to this phase, as patients unable to achieve ROSC rarely survive.

The refractory ACLS phase may then require alternative approaches to optimize perfusion, oxygenation, and ventilation as a bridge to advanced supportive therapies such as ECPR. This study suggests that patients with refractory cardiac arrest may benefit from ETI. The metabolic effects of the low flow state of cardiac arrest likely change the physiologic effects of treatments over time. Hypoventilation may exacerbate these pathophysiologic effects. Importantly, the timing and method of protocolized transition from early to refractory ACLS requires prospective investigation. Other changes to CPR strategy, medication management, and defibrillation may also be beneficial though these were not assessed in this study.

This study was not structured to investigate the cause of worsened oxygenation and ventilation observed in the SGA group. However, breaths given asynchronously with respect to chest compressions may leak around the SGA cuff leading to diminished ventilation and oxygenation. The endotracheal tube is hypothesized to have less leak. Prolonged CPR magnifies slowly accumulating deficiencies in ventilation resulting in severe respiratory acidosis that may worsen acidemia over time.[12] Therefore, it is hypothesized that the combination of more efficient oxygenation and ventilation combined with high quality CPR may account for the improved ABG results and neurologically favorable survival observed in the ETI patients receiving prolonged CPR.

The risks of advanced airway management must also be considered. Airway expertise is an important consideration, as ETI requires additional expertise compared to SGA, and failed ETI attempts are associated with worsened outcomes.[28-30] In the current study, 94% of patients successfully received ETI when ETI was attempted; whereas, the Benger and Wang studies described 69% and 52% rates of successful ETI, respectively. Effects of airway insertion on CPR quality must also be considered. A recent study of the effect of airway management on CPR quality in the PARAMEDIC2 trial demonstrated no effect of airway strategy selection on CPR quality.[31]

This study has important limitations due to study design and patient population. First, this study included patients treated by multiple EMS services in the Twin City metropolitan area with varying intra-arrest airway management strategies and techniques. Without randomization, selection bias related to the airway protocols of specific EMS agencies cannot be excluded. Importantly, ETI and SGA groups had similar baseline and cardiac arrest characteristics. Patients were assigned to their airway group based on the initial airway strategy meaning that patients with failed ETI attempts who converted to SGA remained in the ETI group to avoid bias using an intention-to-treat type design. This may reduce the observed effect size between the groups. The success rate for ETI was high as discussed above. Regional differences in ETI proficiency may impact the relationship with outcomes. All data were gathered by chart review which is susceptible to incomplete documentation of airway attempts or sequential airway strategies. Therefore, data regarding the number of intubation attempts were not available and rate of ETI success could be overestimated. In addition, the ventilation strategy was not specified by the study protocol, so potential effects of 30:2 ventilation vs. asynchronous ventilation cannot be investigated. Further, while this remains the largest published ECPR study in the United States, the limited size of the patient population reduces statistical power of inter-group comparisons, possibly underestimating significance of some differences.

Conclusions

Use of endotracheal intubation as the primary airway strategy in patients with refractory cardiac arrest requiring prolonged CPR was associated with improved oxygenation and ventilation at the time of evaluation for VA-ECMO cannulation as part of an ECPR program. Increased PaO2 upon arrival for VA-ECMO increased eligibility for VA-ECMO. Importantly, endotracheal intubation was associated with increased neurologically favorable survival compared to supraglottic airways in VA-ECMO eligible patients. Further randomized studies are needed to verify the potential benefit of ETI in ECPR patients with refractory cardiac arrest requiring prolonged CPR.

FIGURE LEGENDS

Figure 1: Patient flow diagram for patients treated by the UMN-ECPR program.

Figure 2: Arterial blood results by airway type in all patients. Boxplots depicting the median (solid black horizontal line) and interquartile ranges of the arterial PaO_2 (A), arterial $PaCO_2$ (B), and arterial lactic acid (C) collected at the time of patient arrival to the ECMO cannulation center and evaluation for VA-ECMO cannulation. Red horizontal lines in (A) and (C) represent the protocolized boundaries of PaO_2 and lactic acid, respectively, that determine VA-ECMO eligibility.

Figure 3: Patient outcomes by airway type in all patients. Patient outcomes are shown as a percent of the overall population separated by primary airway management strategy employed by the prehospital ACLS team.

References

1. Panchal AR, Bartos JA, Cabanas JG, Donnino MW, Drennan IR, Hirsch KG, Kudenchuk PJ, Kurz MC, Lavonas EJ, Morley PT, O'Neil BJ, Peberdy MA, Rittenberger JC, Rodriguez AJ, Sawyer KN, Berg KM, Adult B and Advanced Life Support Writing G. 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.

2. Panchal AR, Berg KM, Hirsch KG, Kudenchuk PJ, Del Rios M, Cabanas JG, Link MS, Kurz MC, Chan PS, Morley PT, Hazinski MF and Donnino MW. 2019 American Heart Association Focused Update on Advanced Cardiovascular Life Support: Use of Advanced Airways, Vasopressors, and Extracorporeal Cardiopulmonary Resuscitation During Cardiac Arrest: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2019;140:e881-e894.

3. Jabre P, Penaloza A, Pinero D, Duchateau FX, Borron SW, Javaudin F, Richard O, de Longueville D, Bouilleau G, Devaud ML, Heidet M, Lejeune C, Fauroux S, Greingor JL, Manara A, Hubert JC, Guihard B, Vermylen O, Lievens P, Auffret Y, Maisondieu C, Huet S, Claessens B, Lapostolle F, Javaud N, Reuter PG, Baker E, Vicaut E and Adnet F. Effect of Bag-Mask Ventilation vs Endotracheal Intubation During Cardiopulmonary Resuscitation on Neurological Outcome After Out-of-Hospital Cardiorespiratory Arrest: A Randomized Clinical Trial. *JAMA*. 2018;319:779-787.

4. Benger JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, Nolan JP, Reeves BC, Robinson M, Scott LJ, Smartt H, South A, Stokes EA, Taylor J, Thomas M, Voss S, Wordsworth S and Rogers CA. Effect of a Strategy of a Supraglottic Airway Device vs Tracheal Intubation During Out-of-Hospital Cardiac Arrest on Functional Outcome: The AIRWAYS-2 Randomized Clinical Trial. *JAMA*. 2018;320:779-791.

5. Wang HE, Schmicker RH, Daya MR, Stephens SW, Idris AH, Carlson JN, Colella MR, Herren H, Hansen M, Richmond NJ, Puyana JCJ, Aufderheide TP, Gray RE, Gray PC, Verkest M, Owens PC, Brienza AM, Sternig KJ, May SJ, Sopko GR, Weisfeldt ML and Nichol G. Effect of a Strategy of Initial Laryngeal Tube Insertion vs Endotracheal Intubation on 72-Hour Survival in Adults With Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA*. 2018;320:769-778.

6. Reynolds JC, Grunau BE, Elmer J, Rittenberger JC, Sawyer KN, Kurz MC, Singer B, Proudfoot A and Callaway CW. Prevalence, natural history, and time-dependent outcomes of a multi-center North American cohort of out-of-hospital cardiac arrest extracorporeal CPR candidates. *Resuscitation*. 2017;117:24-31.

7. Grunau B, Puyat J, Wong H, Scheuermeyer FX, Reynolds JC, Kawano T, Singer J, Dick W and Christenson J. Gains of Continuing Resuscitation in Refractory Out-of-hospital Cardiac Arrest: A Model-based Analysis to Identify Deaths Due to Intra-arrest Prognostication. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors*. 2017:1-10.

8. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC and Callaway CW. Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest: Implications for Prolonging or Terminating Resuscitation. *Circulation*. 2016;134:2084-2094.

9. Grunau B, Reynolds JC, Scheuermeyer FX, Stenstrom R, Pennington S, Cheung C, Li J, Habibi M, Ramanathan K, Barbic D and Christenson J. Comparing the prognosis of those with

initial shockable and non-shockable rhythms with increasing durations of CPR: Informing minimum durations of resuscitation. *Resuscitation*. 2016;101:50-6.
10. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, Collins G, Zhang L, Kalra R, Kosmopoulos M, John R, Shaffer A, Frascone RJ, Wesley K, Conterato M, Biros M, Tolar J and Aufderheide TP. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet*. 2020;396:1807-1816.
11. Bartos JA, Frascone RJ, Conterato M, Wesley K, Lick C, Sipprell K, Vuljaj N, Burnett A, Peterson BK, Simpson N, Ham K, Bruen C, Woster C, Haley KB, Moore J, Trigger B, Hodgson L, Harkins K, Kosmopoulos M, Aufderheide TP, Tolar J and Yannopoulos D. The Minnesota mobile extracorporeal cardiopulmonary resuscitation consortium for treatment of out-of-hospital refractory ventricular fibrillation: Program description, performance, and outcomes. *EClinicalMedicine*. 2020;29-30:100632.
12. Bartos JA, Grunau B, Carlson C, Duval S, Ripeckyj A, Kalra R, Raveendran G, John R, Conterato M, Frascone RJ, Trembley A, Aufderheide TP and Yannopoulos D. Improved Survival with Extracorporeal Cardiopulmonary Resuscitation Despite Progressive Metabolic Derangement Associated with Prolonged Resuscitation. *Circulation*. 2020.
13. Lamhaut L, Hutin A, Puymirat E, Jouan J, Raphalen JH, Jouffroy R, Jaffry M, Dagron C, An K, Dumas F, Marijon E, Bougouin W, Tourtier JP, Baud F, Jouven X, Danchin N, Spaulding C and Carli P. A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: An observational study and propensity analysis. *Resuscitation*. 2017;117:109-117.
14. Stub D, Bernard S, Pellegrino V, Smith K, Walker T, Sheldrake J, Hockings L, Shaw J, Duffy SJ, Burrell A, Cameron P, Smit de V and Kaye DM. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation*. 2015;86:88-94.
15. Yannopoulos D, Bartos JA, Martin C, Raveendran G, Missov E, Conterato M, Frascone RJ, Trembley A, Sipprell K, John R, George S, Carlson K, Brunsvold ME, Garcia S and Aufderheide TP. Minnesota Resuscitation Consortium's advanced perfusion and reperfusion cardiac life support strategy for out-of-hospital refractory ventricular fibrillation. *J Am Heart Assoc*. 2016;5:e003732.
16. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, John R, Connett J, Benditt DG, Lurie KG, Wilson RF and Aufderheide TP. Coronary artery disease in patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. *Journal of the American College of Cardiology*. 2017;70:1109-1117.
17. Yannopoulos D, Kalra R, Kosmopoulos M, Walser E, Bartos JA, Murray TA, Connett JE and Aufderheide TP. Rationale and methods of the Advanced R(2)Eperfusion STrategies for Refractory Cardiac Arrest (ARREST) trial. *American heart journal*. 2020;229:29-39.
18. Bartos JA, Carlson K, Carlson C, Raveendran G, John R, Aufderheide TP and Yannopoulos D. Surviving refractory out-of-hospital ventricular fibrillation cardiac arrest: Critical care and extracorporeal membrane oxygenation management. *Resuscitation*. 2018;132:47-55.
19. Gutierrez A, Carlson C, Kalra R, Elliott AM, Yannopoulos D and Bartos JA. Outcomes associated with delayed enteral feeding after cardiac arrest treated with veno-arterial extracorporeal membrane oxygenation and targeted temperature management. *Resuscitation*. 2021;164:20-26.

20. Bougouin W, Dumas F, Lamhaut L, Marijon E, Carli P, Combes A, Pirracchio R, Aissaoui N, Karam N, Deye N, Sideris G, Beganton F, Jost D, Cariou A, Jouven X and Sudden Death Expertise Center i. Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. *European heart journal*. 2019.
21. Hsu CH, Meurer WJ, Domeier R, Fowler J, Whitmore SP, Bassin BS, Gunnerson KJ, Haft JW, Lynch WR, Nallamothu BK, Havey RA, Kidwell KM, Stacey WC, Silbergleit R, Bartlett RH and Neumar RW. Extracorporeal Cardiopulmonary Resuscitation for Refractory Out-of-Hospital Cardiac Arrest (EROCA): Results of a Randomized Feasibility Trial of Expedited Out-of-Hospital Transport. *Annals of emergency medicine*. 2021;78:92-101.
22. Wengenmayer T, Rombach S, Ramshorn F, Biever P, Bode C, Duerschmied D and Staudacher DL. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). *Critical care*. 2017;21:157.
23. Rob D, Smalcova J, Smid O, Kral A, Kovarnik T, Zemanek D, Kavalkova P, Huptych M, Komarek A, Franek O, Havranek S, Linhart A and Belohlavek J. Extracorporeal versus conventional cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: a secondary analysis of the Prague OHCA trial. *Critical care*. 2022;26:330.
24. Wang HE, Szydlo D, Stouffer JA, Lin S, Carlson JN, Vaillancourt C, Sears G, Verbeek RP, Fowler R, Idris AH, Koenig K, Christenson J, Minokadeh A, Brandt J, Rea T and Investigators ROC. Endotracheal intubation versus supraglottic airway insertion in out-of-hospital cardiac arrest. *Resuscitation*. 2012;83:1061-6.
25. McMullan J, Gerecht R, Bonomo J, Robb R, McNally B, Donnelly J, Wang HE and Group CS. Airway management and out-of-hospital cardiac arrest outcome in the CARES registry. *Resuscitation*. 2014;85:617-22.
26. Benoit JL, Gerecht RB, Steuerwald MT and McMullan JT. Endotracheal intubation versus supraglottic airway placement in out-of-hospital cardiac arrest: A meta-analysis. *Resuscitation*. 2015;93:20-6.
27. Hasegawa K, Hiraide A, Chang Y and Brown DF. Association of prehospital advanced airway management with neurologic outcome and survival in patients with out-of-hospital cardiac arrest. *JAMA*. 2013;309:257-66.
28. Kim J, Kim K, Kim T, Rhee JE, Jo YH, Lee JH, Kim YJ, Park CJ, Chung HJ and Hwang SS. The clinical significance of a failed initial intubation attempt during emergency department resuscitation of out-of-hospital cardiac arrest patients. *Resuscitation*. 2014;85:623-7.
29. Wnent J, Franz R, Seewald S, Lefering R, Fischer M, Bohn A, Walther JW, Scholz J, Lukas RP, Grasner JT and German Resuscitation Registry Study G. Difficult intubation and outcome after out-of-hospital cardiac arrest: a registry-based analysis. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2015;23:43.
30. Murphy DL, Bulger NE, Harrington BM, Skerchak JA, Counts CR, Latimer AJ, Yang BY, Maynard C, Rea TD and Sayre MR. Fewer tracheal intubation attempts are associated with improved neurologically intact survival following out-of-hospital cardiac arrest. *Resuscitation*. 2021;167:289-296.
31. Deakin CD, Nolan JP, Ji C, Fothergill RT, Quinn T, Rosser A, Lall R and Perkins GD. The Effect of Airway Management on CPR Quality in the Paramedic2 Randomised Controlled Trial. *Resuscitation*. 2020.

Credit Author Statement

Jason A. Bartos MD, PhD: Conceptualization, Methodology, Investigation, Resources, Writing-Original Draft, Writing- Review and Editing, Supervision, Project Administration
Arianne Clare Agdamag MD: Conceptualization, Methodology, Investigation, Writing-Original Draft
Rajat Kalra MBChB, MS: Methodology, Investigation, Writing-Original Draft, Writing- Review and Editing
Lindsay Nutting DNP: Investigation, Writing- Review and Editing
R.J. Frascone MD: Investigation, Resources, Writing- Review and Editing
Aaron Burnett MD: Investigation, Resources, Writing- Review and Editing
Nik Vuljaj MD: Investigation, Resources, Writing- Review and Editing
Charles Lick MD: Investigation, Resources, Writing- Review and Editing
Peter Tanghe MD: Investigation, Resources, Writing- Review and Editing
Ryan Quinn: Investigation, Resources, Writing- Review and Editing
Nicholas Simpson MD: Investigation, Resources, Writing- Review and Editing
Bjorn Peterson MD: Investigation, Resources, Writing- Review and Editing
Kari Haley MD: Investigation, Resources, Writing- Review and Editing
Kevin Sipprell MD: Investigation, Resources, Writing- Review and Editing
Demetris Yannopoulos MD: Conceptualization, Methodology, Investigation, Resources, Writing- Review and Editing, Supervision

Table 1: Patient and Arrest Characteristics

	Overall (N = 383)	ETI (N = 179)	SGA (N = 204)	p-value
Age, y, SD	57.23 ± 11.9	57.3 ± 12.4	57.2 ± 11.4	0.91
Sex (male), n (%)	311 (81.2)	144 (80.5)	167 (81.9)	0.79
Race				
White, n (%)	308 (80.4)	142 (79.3)	166 (81.4)	0.88
Black, n (%)	39 (10.2)	19 (10.6)	20 (9.8)	
Other, n (%)	36 (9.4)	18 (10.1)	18 (8.8)	
Arrest Characteristics				
Witnessed Arrest, n (%)	295 (77.0)	138 (77.1)	157 (77.0)	1.00
Bystander CPR, n (%)	267 (69.7)	132 (73.7)	135 (66.2)	0.12
Duration of Professional CPR, min, SD	61.9 ± 19.8	62.8 ± 21.2	61.1 ± 18.5	0.39

Categorical variables are presented as counts with proportions. Continuous variables are presented as means ± standard deviations. The p value reflects the comparisons between the airway groups.

Legend: CPR, cardiopulmonary resuscitation; ETI, endotracheal intubation; SGA, supraglottic airway

Table 2: Associations between airway management strategy and patient outcomes and arterial blood results.

	Overall	ETI	SGA	p-value
Arterial Blood Values Upon Patient Arrival to Cannulation Center				
	Overall (n = 383)	ETI (n = 179)	SGA (n = 204)	
$ETCO_2$ (mmHg)	35.0 (25.0, 44.0)	35.0 (26.0, 45.0)	34.0 (25.0, 42.5)	0.84
pH	6.99 (6.85, 7.15)	7.03 (6.90, 7.19)	6.93 (6.80, 7.09)	**<0.001***
$PaCO_2$ (mmHg)	63.0 (46.0, 89.0)	55.0 (42.8, 74.5)	75.0 (52.5, 94.0)	**<0.001***
PaO_2 (mmHg)	65.0 (47.0, 93.0)	70.5 (51.0, 105.0)	58.0 (43.0, 88.0)	**0.001***
Bicarbonate (mmol/L)	16.0 (13.0, 20.0)	16.0 (13.0, 20.0)	16.0 (13.0, 20.0)	0.43
Lactic Acid (mmol/L)	11.9 (9.1, 15.2)	11.8 (8.2, 15.3)	12.0 (9.4, 15.1)	0.35
Failed Resuscitation Continuation Criteria				
	Overall (n = 383)	ETI (n = 179)	SGA (n = 204)	
PaO_2 < 50 mmHg, n (%)	76 (19.8)	23 (12.8)	53 (26.0)	**0.001***
Lactic Acid > 18 mmol/L, n (%)	20 (5.2)	5 (2.8)	15 (7.4)	0.06
$ETCO_2$ < 10 mmHg, n (%)	2 (0.5)	1 (0.6)	1 (0.5)	1.00
VA-ECMO Eligibility Due to Resuscitation Continuation Criteria (PaO_2, lactic acid, $ETCO_2$)				
	Overall (n = 383)	ETI (n = 179)	SGA (n = 204)	
Eligible, n (%)	302 (78.9)	152 (84.9)	150 (73.5)	**0.008***
Ineligible, n (%)	81 (21.1)	27 (15.1)	54 (26.5)	
Patient Outcomes for Patients Eligible for VA-ECMO				
	Overall (n = 302)	ETI (n = 152)	SGA (n = 150)	
CPC 1-2, n (%)	108 (35.8)	64 (42.1)	44 (29.3)	**0.02***
CPC 3-5, n (%)	194 (64.2)	88 (57.9)	106 (70.7)	

Categorical variables are presented as counts with proportions. Continuous variables are presented as median (interquartile range). The p value reflects the comparisons between the airway groups. *indicates statistically significant differences.

Legend: VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CPC, cerebral performance category; $ETCO_2$, end-tidal CO_2; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; ETI, endotracheal intubation; SGA, supraglottic airway

Figure1

Figure 1: Patient Flow Diagram

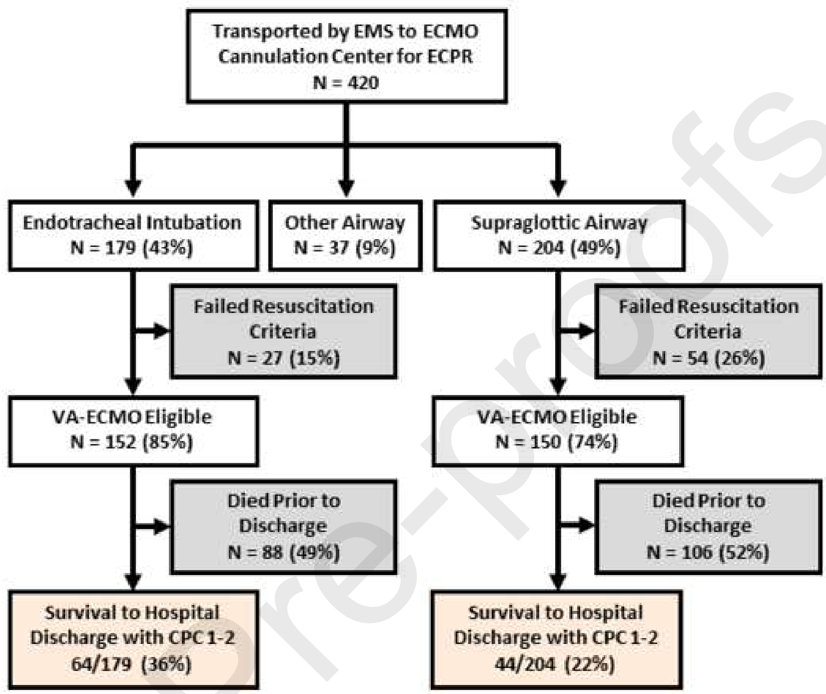


Figure2

Figure 2: Arterial blood results by airway type

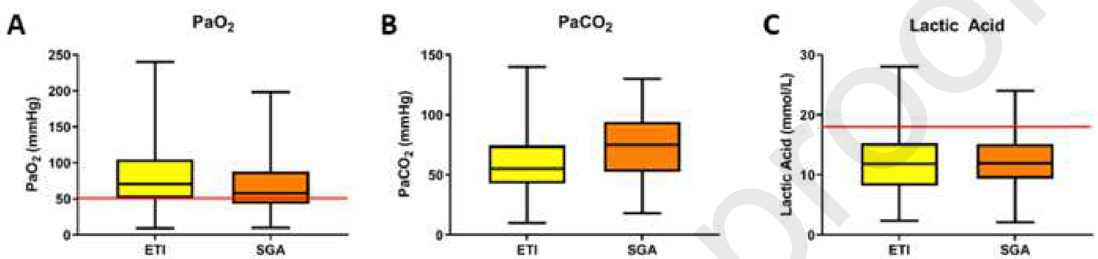
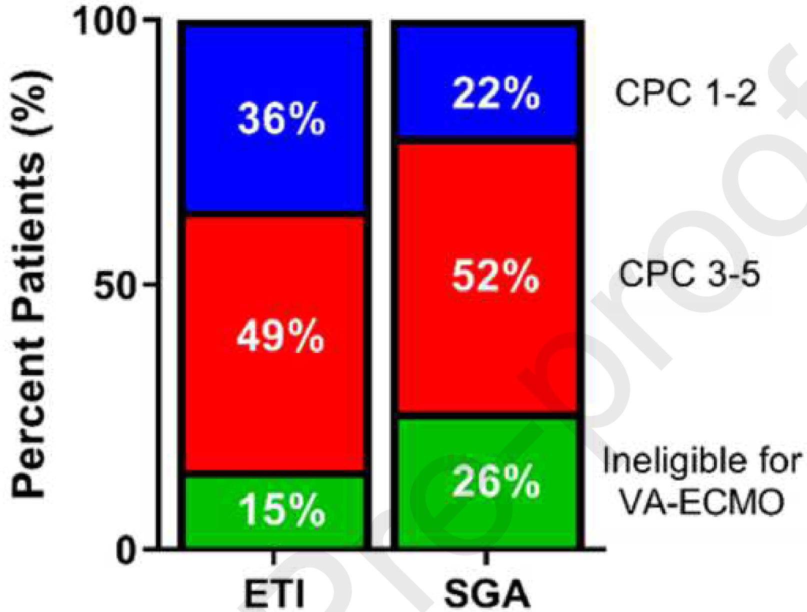


Figure3

Figure 3: Patient outcomes by airway type



<u>CONFLICTS OF INTEREST</u>

None of the authors have any financial or personal relationships with people or organizations that could have inappropriately influenced this work.