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Resuscitation from Out-of-Hospital Cardiac Arrest - When is $EtCO_2$ Reliably Associated with ROSC?

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Abstract

Background: Exhaled end-tidal CO2 ($EtCO_2$) trajectory is associated with out-of-hospital cardiac arrest (OHCA) outcomes. However, the minimum $EtCO_2$ monitoring duration needed to discriminate return of spontaneous circulation (ROSC) from non-ROSC remains unknown. We sought to determine the $EtCO_2$ trajectory observation time required to differentiate ROSC from non-ROSC patients.

Methods: We performed a secondary analysis of the cluster-randomized Pragmatic Airway Resuscitation Trial (PART), which assessed endotracheal intubation or laryngeal tube strategies in OHCA resuscitation. We summarized mean $EtCO_2$ in 1-minute epochs over the resuscitation. Cases were stratified a priori by 1) witnessed vs. unwitnessed status and 2) initial $EtCO_2$: low (≤30 mmHg), moderate (31–49), and high (≥50). Within each stratum, group-based trajectory modeling (GBTM) was used to identify latent $EtCO_2$ trajectory classes, and patients were categorized into

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upward or downward trajectory. To balance trajectory groups on baseline characteristics including age, sex, race, initial rhythm, location, and bystander CPR, we applied inverse probability of treatment weighting. We fit weighted pooled logistic regression models to estimate risk ratios (RR) for ROSC comparing upward vs downward $EtCO_2$ trajectories. Within each stratum, we identified the earliest minute when confidence intervals (CIs) between upward vs downward $EtCO_2$ trajectories no longer overlapped.

Results: $EtCO_2$ data were available for 1,168 patients; 452 (38.6%) witnessed and 716 (61.1%) unwitnessed. Patients were predominantly male (63.5%), with a median age of 65 years (Q1,Q3: 53–75), majority white race (51.3%), and presenting in a non-public setting (85.4%). Overall ROSC was 18.2%: 30.5% of witnessed and 10.5% of unwitnessed. Among witnessed arrests, 95% CI for upward vs. downward $EtCO_2$ trajectories no longer overlapped at 8 minutes for low initial $EtCO_2$ (RR=3.06, 95% CI=1.49, 6.71), 12 minutes for moderate $EtCO_2$ (RR=1.95, 95% CI=1.23, 3.48), and 21 minutes for high $EtCO_2$ (RR=2.12, 95% CI=1.30, 3.73). Among unwitnessed arrests, non-overlapping CIs were first observed at 7 minutes (RR=3.56, 95% CI=1.53, 10.37).

Conclusions: Depending on witness status and initial $EtCO_2$, between 7 and 21 minutes of monitoring are needed to reliably differentiate upward from downward $EtCO_2$ trajectories during OHCA resuscitation. Dynamic $EtCO_2$ trajectory monitoring may provide early prognostic information to guide resuscitation.

Keywords

End-tidal capnography; cardiac arrest resuscitation; outcomes

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of morbidity and mortality. [1–3] Despite significant efforts to improve resuscitation performance through focused initiatives on improving bystander cardiopulmonary resuscitation (CPR), early defibrillation and post-arrest therapeutics, survival has remained poor.[4–6] Cardiac arrest is a dynamic process with ongoing physiologic changes. One mechanism that may enhance survival is better understanding the dynamic physiologic changes that occur during cardiac arrest. The urgency for actionable, real-time information is important given that emergency medical services (EMS) are encouraged to aggressively resuscitation patients on scene to improve outcomes.[7–9]

Real-time bio-signal assessment could provide important insight during cardiac resuscitation. Early warning systems utilizing 48-hour heart rate, respiratory rate and minimum diastolic blood pressure have been used for in-hospital prediction of cardiac arrest.[10,11] These are not feasible bio-signals during ongoing attempted resuscitation of OHCA. As an option during ongoing resuscitation, American Heart Association recommends end-tidal carbon dioxide ($EtCO_2$) capnography during resuscitation from OHCA.[6,12] Recent studies have found that dynamic changes in $EtCO_2$ throughout resuscitation are associated with subsequent outcomes. [13–16] Specifically, an increasing capnography trajectory over resuscitation is most strongly associated with return of spontaneous circulation (ROSC).[13] Determination of an upward vs downward capnography trajectory is an important initial step. Beyond capnography trajectory pattern, questions on how long a trajectory must be observed remain unanswered. As resuscitation decisions are immediate and occur often in the prehospital space, understanding the performance of $EtCO_2$ time-driven trajectories during active resuscitation may assist in guiding resuscitation decisions.

In support of the utility of dynamic $EtCO_2$ analysis, an important gap is the minimum observation time needed to affirm the certainty of these trajectories. In this study we sought to determine the observation time needed to differentiate upward from downward capnography trajectories during resuscitation from OHCA.

Methods

Study Design, Setting, Participants

We performed a secondary analysis of the Pragmatic Airway Resuscitation Trial (PART).[17] PART (NCT02419573) evaluated the effectiveness of advanced airway devices on 72-hour survival in adult (age ≥ 18 years) non-traumatic OHCA. PART involved cluster cross-over randomization of laryngeal tube or endotracheal intubation for airway advanced airway management across 27 emergency medical services (EMS) agencies from five communities of the Resuscitation Outcomes Consortium. Data was collected from December 1st, 2015, through November 4th, 2017. For this analysis, we only included subjects with any $EtCO_2$ recorded. The Institutional Review Board of The Ohio State University approved this secondary analysis of the parent trial. PART trial data is available through NHLBI BioLINCC data repository.

Measures

Our primary measure was capnometry. EMS agencies collected continuous capnography waveforms and $EtCO_2$ readings using portable cardiac defibrillator monitors (Physio-Control, Inc.: LifePak 15 series, Physio-Control, Redmond, Washington; Zoll, Inc.:X-series, Zoll Medical Coorporation, Inc., Chelmsford, Massachusetts; or Philips, Inc.: MRx series, Philips Healthcare, Andover, Massachusetts).

Maximal $EtCO_2$ values per ventilation were annotated using previously validated automated signal processing with manual review in a custom graphical user interface implemented in MATLAB (Mathworks, Inc., Natick, MA).[18–20] Mean $EtCO_2$ was summarized one-minute (min) epochs from the start of resuscitation through the end of the event. We included all cases with >50% interpretable $EtCO_2$ signals in at least two epochs.

Outcomes

The primary outcome was return of spontaneous circulation (ROSC), defined as sustained spontaneous circulation without chest compressions at EMS arrival to the receiving emergency department and hospital admission from the ED. Any ROSC was determined by clinical evaluation in the parent trial.[21]

Analysis

Trajectory Modeling: Our objective was to identify the earliest time point when upward from downward capnography trajectories could be distinguished with respect to ROSC. We used group-based trajectory modeling (GBTM) to characterize $EtCO_2$ changes during the first 30 minutes of resuscitation. Trajectory models were fit separately for unwitnessed arrests and witnessed arrests, given the differences in time reliability between strata. Within main strata, we further stratified by initial $EtCO_2$: 1) low≤30 mmHg, 2) moderate=31–49 mmHg, and 3) high≥50 mmHg. We elected to have two groups (upward vs downward trajectory) selected based on both statistical fit and clinical interpretability. Each patient was then assigned to one of the two trajectory groups corresponding to their highest posterior probability.

Propensity Score Estimation and Inverse Probability of Treatment Weighting: Trajectory group assignment (upward vs downward) was modeled using a propensity score (PS) approach that included age, sex (male/female), race (White/Black/other), initial rhythm (shockable/non-shockable), arrest location (public/non-public), and bystander CPR (yes/no). Stabilized inverse probability of treatment weighting (IPTW) were calculated and applied to reduce baseline inbalances across trajectory groups.[22]

Pooled Logistic Regression and Bootstrapping: We fit stabilized IPTW pooled logistic regression (PLR) models to estimate the temporal association between $EtCO_2$ trajectory group and ROSC. Models included time terms interactions with trajectory group to permit time-varying associations. As a sensitivity analysis, we included final airway management as an additional covariate in our PLR models. To obtain 95% confidence intervals (CI), we implemented nonparametric bootstrapping with 1,000 replicates. For each bootstrap sample, PLR models were refit, predicted hazards were obtained, and risk functions were estimated at each minute of $EtCO_2$ measurement. From these, we derived risk ratios (RR) and 95% CI comparing upward vs downward $EtCO_2$ trajectories.

Results Interpretation: Within each strata, we identified the earliest minute at which the 95% CIs for upward capnography trajectories did not overlap with 95% CIs for downward capnography trajectories. We report the risk ratio and 95% confidence intervals (CI) at the identified minute for each strata. All statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Capnography recordings with timing information were available for 1,172 (39.0%) patients of 3,004 patients enrolled in the parent trial. Of these, 452 (38.6%) were witnessed arrests and 716 (61.1%) were unwitnessed arrests (Figure 1). Overall ROSC was 18.2%. Included cases reflected a typical OHCA patient in the United States: predominantly male (63.5%), median age of 65 years (Q1, Q3: 53–75), majority white race (51.3%), and most presenting with a non-shockable rhythm (71.5%) in a non-public setting (85.4%) (Table 1).

Among the 452 witnessed arrests, 190 (42.0%) had a low initial $EtCO_2$, 161 (35.6% had a moderate initial $EtCO_2$, and 101 (22.4%) had a high initial $EtCO_2$. Among patients with a witnessed arrest and low initial EtCO2 (≤30 mmHg), those in the upward trajectory group had more than a threefold probability of ROSC compared with those in the downward group (RR=3.06, 95% CI=1.49, 6.71). This divergence between upward and downward trajectories became apparent after 8 minutes of resuscitation (Figure 2A).

Among patients with a witnessed arrest and moderate initial capnography (31–50 mmHg), those in the upward trajectory group had nearly twice the probability of ROSC compared with the downward group (RR=1.95, 95% CI=1.23, 3.48), with non-overlapping CIs first observed at 12 minutes (Figure 2B).

Among patients with a witnessed arrest and high initial capnography (≥50mmHg), the upward trajectory group had over double the probability of ROSC compared with those in the downward group (RR=2.12, 95% CI=1.30, 3.73). This separation of trajectories occurred later, at 21 minutes of $EtCO_2$ monitoring (Figure 2C).

Due to similar trajectory patterns across strata, all unwitnessed cases were modeled together. Patients in the upward trajectory group had 3.6 times the probability of ROSC compared with those in the downward group (RR=3.56; 95% CI=1.53, 10.37). This separation between groups occurred after 7 minutes of $EtCO_2$ monitoring (Figure 3).

Overall, depending on initial $EtCO_2$ level and witness status, between 7 and 21 minutes of resuscitation were required to clearly differentiate upward from downward $EtCO_2$ trajectories (Figure 4). In sensitivity analysis including final airway type as a covariate in pooled logistic outcome models did not change estimates.

Discussion

Previously, we established that $EtCO_2$ trajectories are associated with outcomes from cardiac arrest.[13] The current study builds upon these findings, demonstrating that anywhere from 7 to 21 minutes of continuous $EtCO_2$ observation time is required to clearly differentiate upward vs downward trajectories associated with ROSC. Other important initial characteristics included witnessed status and initial capnography value. Incorporating dynamic time-varying changes in $EtCO_2$ may serve as a guide for prehospital resuscitation.

Initial observational studies without capnography suggested a minimum of 30 to 40 minutes of resuscitation time should be performed prior to termination decisions.[23] We previously showed that dynamic capnography changes over resuscitation are associated with OHCA outcomes. [13,15,16] The current study answers a simple but very important question; how long must rescuers observe $EtCO_2$ trajectories to meaningfully distinguish upwards from downwards capnography patterns? Depending on witnessed status and initial $EtCO_2$, these findings emphasize that EMS providers should perform minimally 7 to 21 minutes of monitored resuscitation with capnography before considering decisions on resuscitation efforts. Notably, these times align with other prior observational cardiac arrest studies.[24] This study may aid decision making intra-arrest, as both short (5–15 minutes) and prolonged (>20 minutes) resuscitation efforts have shown comparable outcomes in observational cardiac arrest studies.[25] Identifying who may benefit from extended resuscitation versus characteristics associated with worse outcomes could meaningfully inform and impact resuscitation decisions.

This simple but important question lays the foundation for practical clinical applications. For example many existing EMS cardiac arrest guidelines focus on termination decisions. Application of capnography trajectories in guidelines may better inform and modify termination of resuscitation decisions.[26–28] Existing termination of resuscitation decisions based on OHCA clinical characteristics such as witnessed status, bystander interventions, initial rhythm, defibrillation and duration of resuscitation efforts show poor performance with 62% sensitivity for death.[27 29] Recent studies of in-hospital arrest decision algorithms included resuscitation duration greater than 10 minutes for improved algorithm performance.[30] Our findings align with studies suggesting higher termination of resuscitation accuracy with longer periods of observation.

These preliminary findings from one secondary study of randomized control trial do not justify adoption into current termination decision rules. We suggest these findings expand our understanding of real-time bio-signals to guide resuscitation decisions in the prehospital space but recommend caution about incorporating them into implementation of decision rules. Further, prospective validation effort is needed before considering incorporation in clinical practice. Decision rules are terminal decisions in the setting of high ethical complexity.[31,32] Reviewing our data for witnessed arrests with a low initial $EtCO_2$ at 8 minutes of resuscitation, downward capnography trajectory patients still have an 8% (95% CI 4.2% to 12.8%) risk of ROSC at this time-point. This is well above the recommended 1% futility rate for continued efforts.[32] Validation in other cohorts is also required prior to implementation. Overall, these data provide clinical insight into the potential role of dynamic real-time decision tool for the prehospital space.

Further limitations should be considered in interpreting these data. Capnography values in this study were inclusive of bag-valve-mask ventilations. These represent a minority of our cohort, but the validity of bag-valve-mask capnography remains to be confirmed. Although propensity score IPTW adjusted for Utstein criteria, we were unable to incorporate minute-by-minute chest compression and ventilation quality metrics which are known to associate with capnography values. In PART average ventilation rates and chest compression rates were not significantly associated with capnography trajectories and outcomes.[13] Further, we did not incorporate epinephrine or sodium bicarbonate administration in our models which also may affect capnography trajectories. Importantly, divergence times identified in this study are specific for the PART dataset and may not apply to other EMS systems. Early capnography values were unexpectedly higher in our cohort,[13] therefore future validation studies should consider variable time-points. Larger studies may also identify earlier divergence times as the confidence intervals between groups narrows with larger cohorts.

Conclusions

Dynamic capnography trajectories may provide insight to patient-specific OHCA outcomes. In this cohort, upward and downward capnography trajectories could be distinguished between 7 to 21 minutes of resuscitation. Dynamic $EtCO_2$ analysis may be useful for guiding resuscitation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

OHCA	Out-of-Hospital Cardiac Arrest
CBR	cardiopulmonary resuscitation
$EtCO_2$	End-tidal capnography
ROSC	return of spontaneous circulation
EMS	emergency medical services
IPTW	Inverse probability of treatment weighting
PART	Pragmatic Airway Resuscitation Trial

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Clinical Perspective

1. What is new?

- End-tidal capnography trajectories over cardiac resuscitation are different between patients who will achieve return of pulses than patients whom will not.
- Depending on the witnessed status and initial capnography value, anywhere from 7 to 21 minutes of capnography trajectory time is required to differentiate a patient with an upward capnography trajectory from a patient with a downward capnography trajectory.

2. What are the clinical implications?

- Capnography trajectories provide clinical insight into patient outcomes during cardiac resuscitation.
- Although this secondary analysis supports capnography trajectories as a real-time decision tool, validation of time-points and trajectories is required prior to implementation.

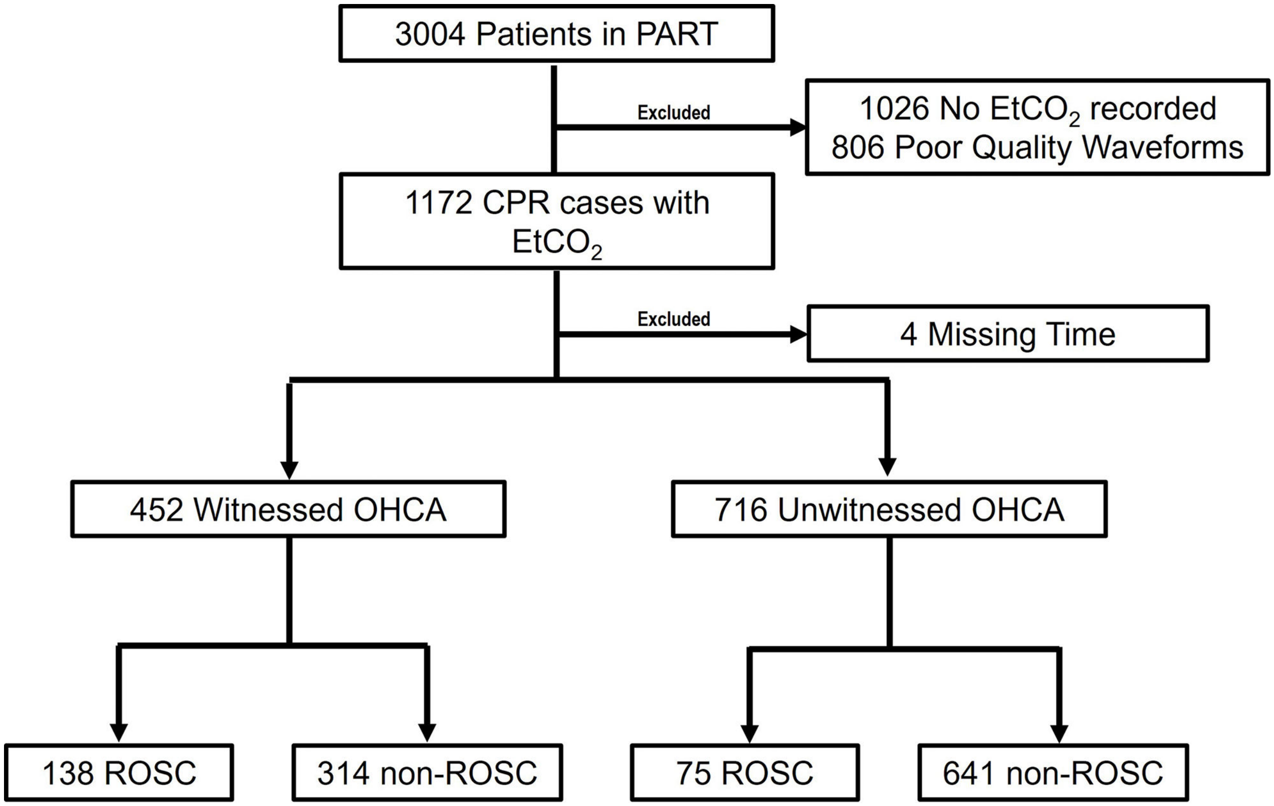

Figure 1: Patient Flow Diagram

A

B

C

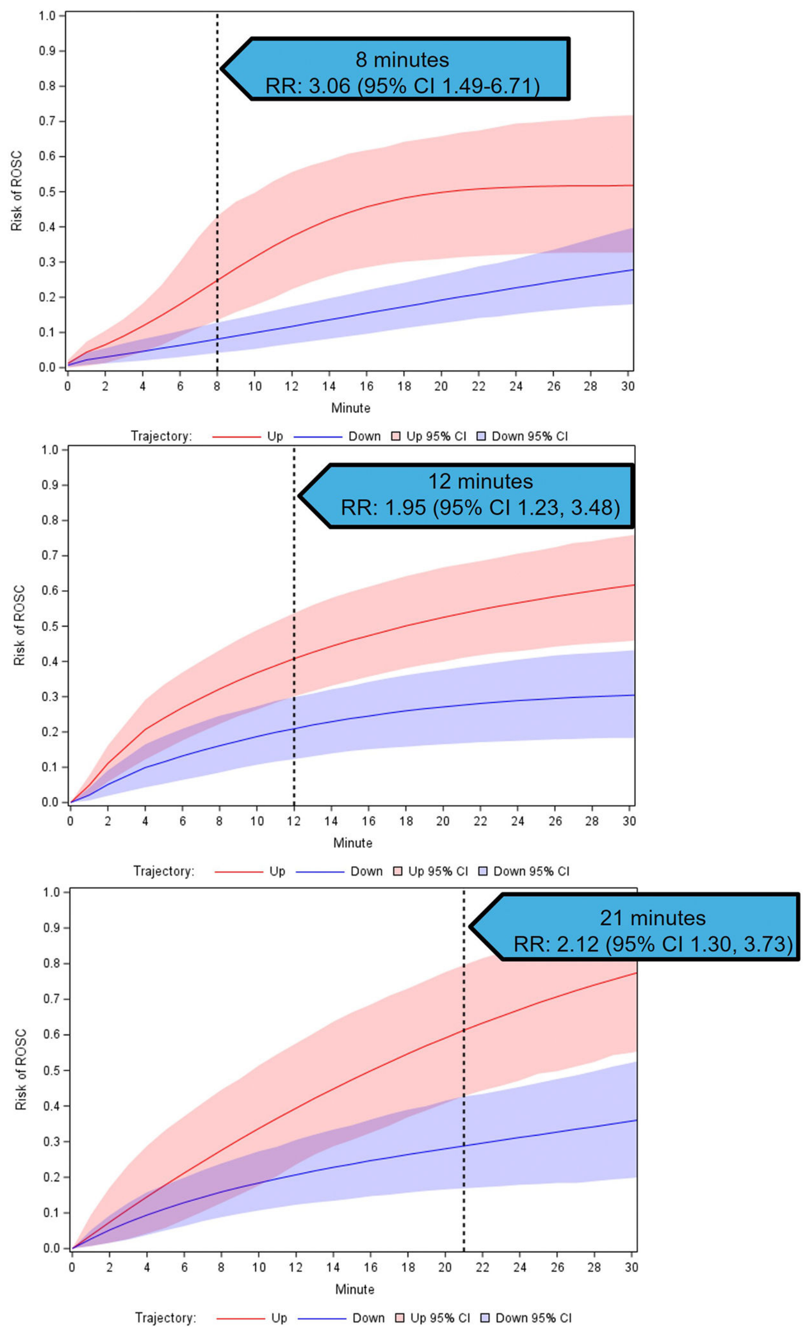

Figure 2: Witnessed Arrests Relative Risk of Return of Spontaneous Circulation (ROSC) by Capnography Trajectory.

Witnessed Cardiac Arrests were categorized into three group based trajectories based on initial capnography values: A) Low = less than 30mmHg, B) Moderate = 30 to 50 mmHg, C) High = greater than 50 mmHg. The risk of ROSC is shown in patients with an upward (pink) or downward (blue) capnography trajectory over time in minutes (min). The relative risk of ROSC (RR) and 95% confidence interval was calculated when upward capnography trajectory patients clearly diverged from downward capnography trajectory patients.

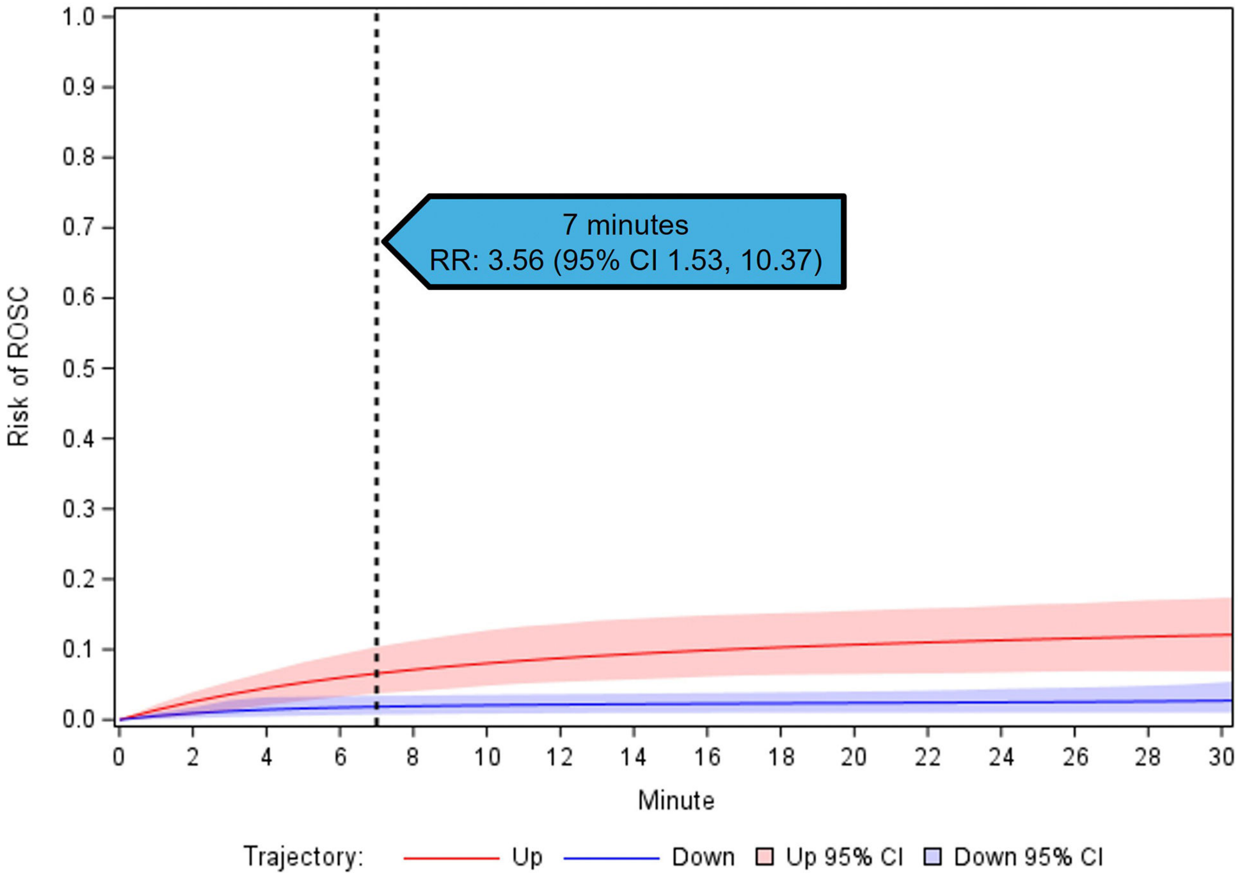

Figure 3: Unwitnessed Arrests Relative Risk of Return of Spontaneous Circulation (ROSC) by Capnography Trajectory.

Unwitnessed cardiac arrests trajectories all performed uniformly. The risk of ROSC is shown in patients with an upward (pink) or downward (blue) capnography trajectory over time in minutes (min). The relative risk of ROSC (RR) and 95% confidence interval was calculated when upward capnography trajectory patients clearly diverged from downward capnography trajectory patients.

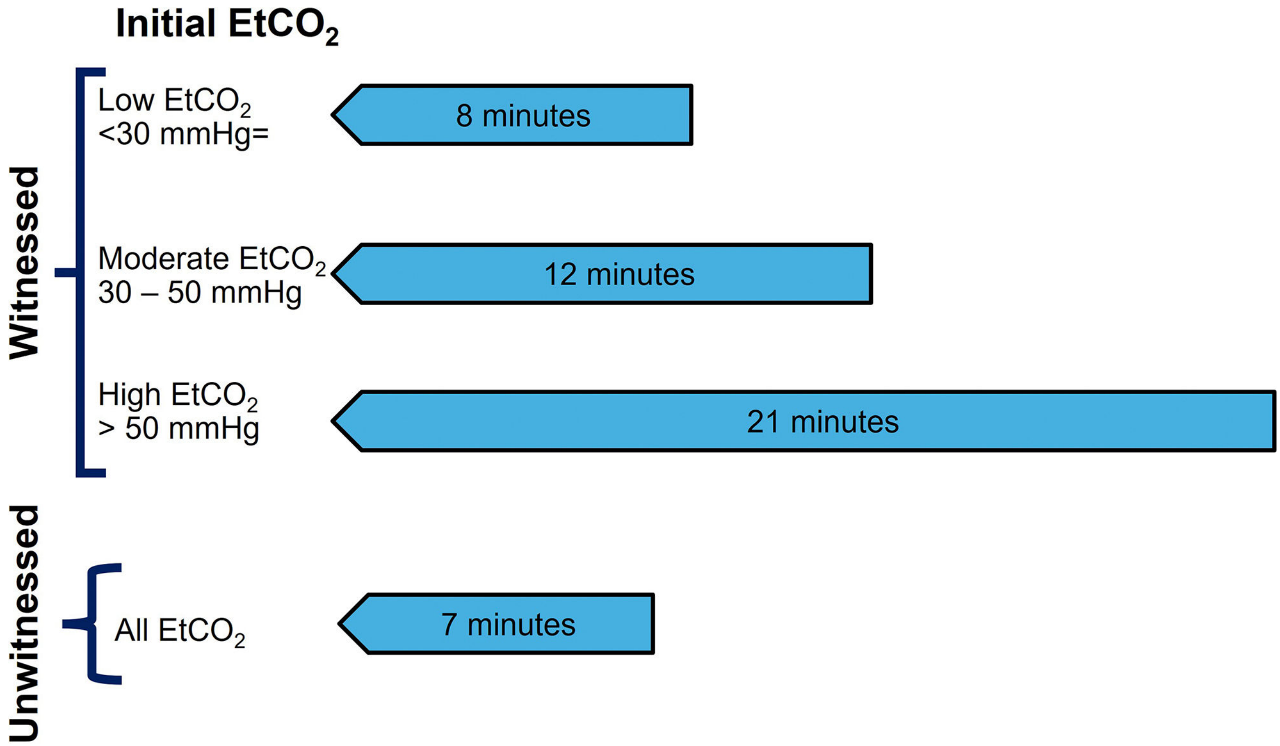

Figure 4: Summary of all Capnography Trajectory Divergence Times

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Table 1:

Demographics

Individual Characteristics	Total n = 1,168	Witnessed n = 452	Unwitnessed n = 716
Age, median (IQR)	64 (52, 75)	65 (53,75)	63 (50,74)
Sex			
Male, n(%)	722 (61.9%)	287 (63.5%)	435 (60.8%)
Female, n (%)	445 (38.1%)	165 (36.5%)	280 (39.2%)
Missing, n (%)	1 (0.0%)	0 (0.0%)	1 (0.0%)
Race n(%)			
White	623 (53.3%)	232 (51.3%)	391 (54.6%)
Black/African-American	294 (25.2%)	107 (23.7%)	187 (26.1%)
Other	120 (10.3%)	53 (11.7%)	67 (9.4%)
Missing	131 (11.2%)	60 (13.3%)	71 (9.9%)
Location of Arrest n(%)			
Public	121 (10.4%)	66 (14.6%)	55 (7.7%)
Nonpublic	1,046 (89.6%)	386 (85.4%)	660 (92.2%)
Missing	1 (0.1%)	0 (0.0%)	1 (0.1%)
Initial rhythm, n(%)			
Shockable	184 (15.8%)	129 (28.5%)	55 (7.7%)
Non-shockable	984 (84.2%)	323 (71.5%)	661 (92.3%)
Bystander CPR n(%)	588 (50.3%)	210 (46.5%)	3,78 (52.8%)
Bystander AED n(%)	128 (11.0%)	46 (10.2%)	82 (11.5%)
ROSC n(%)	213 (18.2%)	138 (30.5%)	75 (10.5%)
72-hour Survival n(%)	128 (11.0%)	94 (20.8%)	34 (4.8%)