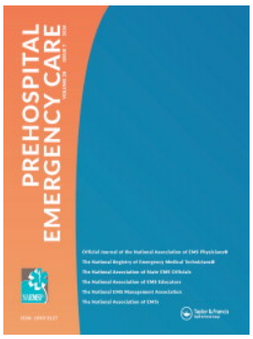

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The Route to ROSC: Evaluating the Impact of Route and Timing of Epinephrine Administration in Out-of-Hospital Cardiac Arrest Outcomes

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ABSTRACT

Objectives: Previous investigations comparing intraosseous (IO) and intravenous (IV) epinephrine delivery in out-of-hospital cardiac arrest (OHCA) suggest that epinephrine is oftentimes more expeditiously administered *via* the IO route, but this temporal benefit doesn't always translate to clinical benefit. However, very few studies adequately controlled for indication and resuscitation time biases, making the influence of first epinephrine route on OHCA outcomes unclear. To determine the association between first epinephrine route and return of spontaneous circulation (ROSC) while controlling for resuscitation time bias and other potential confounders.

Methods: We conducted a retrospective analysis using the 2020 ESO Data Collaborative dataset. Adult patients with a witnessed, non-traumatic OHCA prior to EMS arrival were included. Logistic regression was used to determine the association between medication route and ROSC. Linear regression was then used to calculate the probability of ROSC for each route across all call receipt-to-drug delivery intervals. Using these linear equations, the call receipt-to-drug delivery intervals were calculated that would yield equivalent probabilities of ROSC between the IV and IO routes.

Results: Data were available for 10,350 patients, of which 27.4% presented with a shockable rhythm, 29.7% received bystander CPR, and 39.6% experienced ROSC. After controlling for confounders, IO epinephrine was associated with decreased likelihood of ROSC (OR = 0.77, $p < 0.001$). The linear regression models provided differing slope coefficients for ROSC between each route, with the IV route associated with a higher likelihood of ROSC for any given call receipt-to-drug-delivery interval. From these equations, the additional time allowed to establish an IV and administer epinephrine intravenously beyond the time required for IO delivery, yet with an equivalent predicted probability of ROSC *via* the IO route, was calculated. This additional time interval for intravenous administration declined linearly from 9 min at a call receipt-to-intraosseous epinephrine interval of 4 min to no additional time at a call receipt-to-intraosseous epinephrine interval of 29 min.

Conclusions: This retrospective analysis of a national EMS database revealed that IO epinephrine was negatively associated with ROSC. Additionally, there appears to be a finite time window during which intravenous epinephrine remains superior to the intraosseous route even if there are brief initial delays in IV drug delivery.

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Introduction

Out-of-hospital cardiac arrest (OHCA) results in roughly 347,000 EMS responses annually in the United States (1). The prognostic implications of a witnessed arrest, rapid bystander CPR, and early defibrillation on achieving favorable patient outcomes have been well-described (2–4). When patients do not promptly respond to CPR and defibrillation, current OHCA resuscitation guidelines recommend rapid administration of epinephrine (5). Although the optimum route for epinephrine administration remains uncertain, the guidelines consider intravenous (IV) as the preferred route with the intraosseous (IO) route reserved for cases where IV access is either anticipated to be difficult or proves unsuccessful. However, this is a recommendation based on low levels of evidence.

Several studies have demonstrated that each minute of delay in the delivery of epinephrine is associated with a 2%-6% decline in the rate of return of spontaneous circulation (ROSC) and a 4%-10% decline in the likelihood of survival with favorable neurological outcomes (6–10). In comparison to IV, the IO route may potentially offer earlier drug delivery and improved outcomes due to faster procedural times and a higher first-attempt success rate (11–13). Because of these perceived advantages, recent studies report an increasing trend in IO placement over the past few years (14–15),

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yet several investigations comparing IV and IO delivery routes in OHCA have actually demonstrated worse outcomes with the IO route.

In a retrospective analysis of 1,800 patients in the King County, Washington EMS system, Feinstein et al observed a lower odds of ROSC and survival to hospital admission and a non-significant trend toward lower survival to discharge with IO versus IV epinephrine (16). However, due to overall low IO use in their sample (15%), this study may have been underpowered to detect a difference in discharge rates.

Using data from the Cardiac Arrest Registry to Enhance Survival (CARES) database, Hamam et al evaluated the influence of epinephrine route among the three most populous counties in Michigan (17). In their cohort of 6,869 OHCA patients, they observed lower odds of sustained ROSC, hospital survival, and favorable neurological outcomes when patients received epinephrine intraosseously. Similar results were found in a secondary analysis of 13,155 patients in the Resuscitation Outcomes Consortium Prehospital Resuscitation Using an Impedance Valve and Early Versus Delayed (ROC-PRIMED) data set where IO was found to be unfavorable across all outcome measures (18).

A secondary analysis of the Continuous Chest Compression trial by Mody et al observed no differences in hospital survival or survival with favorable neurological function with IO access when compared to IV (19). However, they did find that epinephrine administered IO was associated with lower rates of sustained ROSC.

In a reanalysis of the Pre-Hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (Paramedic2) trial data, Nolan et al found no difference in treatment effect between the IV and IO routes in the administration of epinephrine or placebo on ROSC, 30-day survival, or neurological outcome at discharge (20). Unique to this study is that IO access was considered only after two failed IV attempts, which introduces an element of resuscitation time bias as IO epinephrine administration would have been delayed in comparison to the IV route.

The conflicting outcomes of these studies notwithstanding, interpretation of these findings is further complicated by a common methodological limitation. Most of these studies did not control for the collapse-to-drug delivery interval or they included patients with unwitnessed arrests, which precludes accurate determination of the collapse-to-drug delivery interval – a factor meaningfully associated with OHCA outcomes. Therefore, using a national EMS database, we sought to develop a model describing the likelihood of ROSC as a function of first epinephrine route while controlling for the collapse-to-drug interval and other potentially confounding variables.

Methods

Study Setting

With Institutional Review Board (IRB) approval from Methodist University, we conducted a retrospective analysis using the 2020 ESO Data Collaborative annual research dataset (ESO Inc., Austin, TX), one of the nation's largest electronic patient care report (ePCR) vendors. The ESO data set included records from over 2,000 EMS agencies in the United States that consented to the release of de-identified data for prehospital research purposes.

Sample Selection

Patients who sustained an OHCA between January 1 and December 31, 2020, were retrospectively identified using the primary impression of cardiac arrest diagnosed by the on-scene paramedic. All adult patients ($\geq$18 years) who experienced a witnessed, non-traumatic cardiac arrest prior to EMS arrival and who received at least one bolus of epinephrine *via* the IV or IO routes were eligible for inclusion.

Prior studies have suggested that an initial vasopressor administration greater than 30 min post-arrest is of questionable effectiveness (6). Consequently, we excluded any patients receiving the first bolus of epinephrine greater than 30 min after call receipt. Also excluded were patients with missing values for any of the relevant data points.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 28 (IBM Corporation; Armonk, New York USA) with statistical significance established at $p \leq 0.05$. Continuous variables are reported as means and standard deviation and were analyzed using Student's t-test. Categorical variables are presented as percentages and were analyzed using Fisher's exact test, chi square test, or chi square test with continuity correction as indicated. The primary outcome was return of spontaneous circulation prior to hospital arrival. Logistic regression was used to obtain adjusted odds ratios for epinephrine route while controlling for potentially confounding variables. These variables were selected *a priori* and included patient age, sex, and non-Caucasian race; bystander CPR; whether the initial rhythm was shockable; arrest etiology; advanced airway use; and call receipt-to-first epinephrine administration interval, which was measured in minutes. For each route, a simple linear regression model was used to identify trends in ROSC rates across call receipt-to-first epinephrine administration strata. Because the exact time of patient collapse is often unknown or undocumented, and because all arrests in our sample were witnessed and would presumably have initiated a prompt call to 9-1-1, we used time of call receipt as a surrogate measure for time of collapse.

As a sensitivity analysis, propensity score matching was used to reduce the effects of indication bias and potentially confounding variables on the comparisons of patients receiving their first epinephrine bolus *via* the IO versus IV route. Propensity scores were calculated using logistic regression with first epinephrine route (IO or IV) as the dependent variable. The independent variables included all of the covariates previously identified for the primary analysis. Patients from the IV group were matched with patients in the IO group in a 1:1 ratio on the basis of propensity scores using

the nearest neighbor matching algorithm with a 0.2 caliper width. To evaluate balance between the IV and IO groups, we calculated absolute standardized differences (ASD) on all covariates after propensity score matching. We considered an ASD < 0.1 among all variables as a well-matched data set. Adjusted odds-ratio of ROSC were obtained from the propensity score matched cohort using a cox logistic regression stratified on the matched pair variable.

Results

During the 2020 calendar year, 106,815 adult patients sustained an OHCA, of which 12,594 met inclusion criteria. In toto, 2,244 (17.8%) were excluded due to missing data, leaving 10,350 patients for subsequent analysis (Figure 1). Of patients included, the mean age was 65.32 (SD = 15.59) years, 63.8% were males, and 26.2% were of non-Caucasian race. The bulk (83.1%) of arrests were of presumed cardiac etiology and roughly one-fourth (27.4%) presented with an initially shockable rhythm. Bystander CPR was performed in 29.7% of cases and 84.8% received an advanced airway (supraglottic or endotracheal intubation). The mean EMS response interval was 7.76 (SD = 3.82) minutes, and the mean call receipt-to-first epinephrine interval was 16.29 (SD = 5.10) minutes. The first epinephrine bolus was administered intravenously in 4,528 (43.8%) of patients while the remaining 5,822 (56.2%) received the drug intraosseously. In total, 4,099 (39.6%) experienced ROSC at some point during the prehospital phase of resuscitation (Table 1).

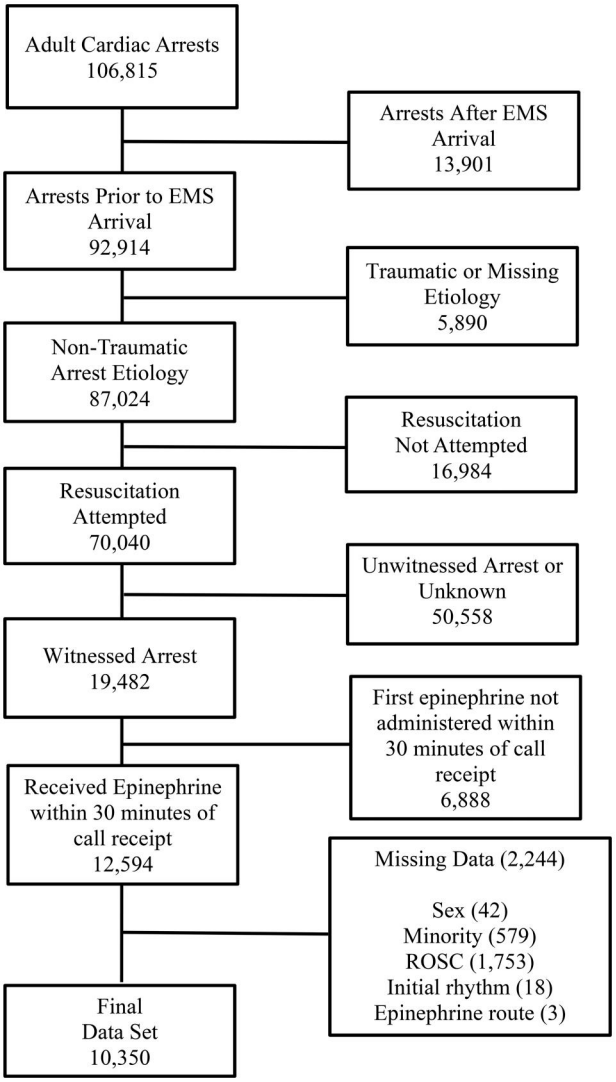

Figure 1. Schematic demonstrating the flow of patients included in the study sample.

The results of the univariate analysis of patients dichotomized by first epinephrine route revealed significant differences in baseline characteristics between the two groups (Table 1). Compared to patients receiving epinephrine intravenously, those receiving epinephrine intraosseously were more likely to be non-Caucasian (27.7% vs. 24.4%, $p < 0.001$) and less likely to be of male sex (62.0% vs. 66.0%, $p < 0.001$), receive bystander CPR (28.8% vs. 30.9%, $p = 0.024$), present with a shockable rhythm (25.8% vs. 29.3%, $p < 0.001$) or attain ROSC (37.1% vs. 42.9%, $p < 0.001$). There were no statistically significant differences in patient age or EMS response time between the groups. However, there was a small, but statistically significant difference favoring the IO route in the mean EMS scene arrival-to-first epinephrine interval (8.04 vs. 8.25 min, $p = 0.007$) and in mean call receipt-to-first epinephrine interval (16.17 vs. 16.45 min, $p = 0.006$).

Because patients were not randomly assigned to the IV or IO group and differences existed in baseline characteristics between the two groups, we used propensity score matching to address the influence of indication bias on the route of first epinephrine administration. We successfully matched 4,528 patients in the IV group with an equal number of patients in the IO group. After matching, the two groups were balanced across all covariates with all ASD < 0.1 (Table 2).

For the primary analysis using the full cohort of patients, logistic regression was used to determine the impact of first epinephrine route on ROSC while controlling for potential confounders. ROSC was less likely when epinephrine was administered intraosseously (OR = 0.77, $p < 0.001$); in males (OR = 0.725, $p < 0.001$); and with increasing call receipt-to-epinephrine interval (OR = 0.96 per minute, $p < 0.001$). Compared to patients with non-shockable rhythms, patients presenting with shockable rhythms were more likely to achieve ROSC (OR = 1.46, $p < 0.001$) as were patients receiving bystander CPR (OR = 1.12, $p = 0.01$) and placement of an advanced airway (OR = 1.33, $p < 0.001$). Compared to patients with a presumed cardiac etiology of arrest, those with respiratory (OR = 1.65, $p < 0.001$) and drug overdose (OR = 1.53, $p = 0.002$) etiologies were more likely to attain ROSC. Age and non-Caucasian race were not independent predictors of prehospital ROSC (Table 3). In the sensitivity analysis using the propensity matched cohort, we obtained results similar to the primary analysis. The exceptions were drug overdose arrest etiology and bystander CPR, which showed trends consistent with the primary analysis but that were no longer statistically significant (Table 3).

Table 1. Baseline patient characteristics stratified by route of first epinephrine administration.

	All Patients ($n = 10,350$)	Intravenous ($n = 4,528$)	Intraosseous ($n = 5,822$)	*p*-value
Age (years, ±SD)	65.32 (± 15.59)	65.56 (± 15.72)	65.13 (± 15.48)	0.161
Male sex (%)	63.8%	66.0%	62.0%	<0.001
Minority (%)	26.2%	24.4%	27.7%	<0.001
Etiology of Arrest				
Presumed Cardiac (%)	83.1%	83.8%	82.5%	0.043
Respiratory (%)	11.5%	10.7%	12.1%	
Drug overdose (%)	2.2%	2.5%	2.0%	
Other (%)	3.2%	3.0%	3.4%	
Received bystander CPR (%)	29.7%	30.9%	28.8%	0.024
Initial shockable rhythm (%)	27.4%	29.3%	25.8%	<0.001
Received advanced airway placement (%)	84.8%	84.5%	85.0%	0.443
EMS response time (minutes, ±SD)	7.76 (± 3.82)	7.80 (± 3.84)	7.72 (± 3.80)	0.298
EMS scene arrival to first epinephrine interval (minutes, ±SD)	8.13 (± 3.94)	8.25 (± 3.96)	8.04 (± 3.92)	0.007
PSAP call receipt to first epinephrine interval (minutes, ±SD)	16.29 (± 5.10)	16.45 (± 5.10)	16.17 (± 5.10)	0.006
ROSC (%)	39.6%	42.9%	37.1%	<0.001

CPR: Cardiopulmonary Resuscitation; EMS: Emergency Medical Services; PSAP: Public Safety Access Point; ROSC: Return of Spontaneous Circulation; SD: Standard Deviation.

Table 2. Baseline characteristics before and after propensity score matching.

	Complete Sample ($n = 10,350$)			Propensity Score Matched Sample ($n = 9,056$)		
Variable	Intravenous	Intraosseous	ASD	Intravenous	Intraosseous	ASD
Age (per year)	65.56 (± 15.72)	65.13 (± 15.48)	0.03	65.56 (± 15.72)	65.19 (± 15.54)	0.02
Male sex (n, %)	2,990 (66.0%)	3,612 (62.0%)	0.08	2,990 (66.0%)	2,813 (62.1%)	0.08
Minority (n, %)	1,104 (24.4%)	1,611 (27.7%)	0.08	1,104 (24.4%)	1,257 (27.8%)	0.08
Etiology of Arrest (n, %)						
Presumed Cardiac	3,793 (83.8%)	4,803 (82.5%)	0.03	3,793 (83.8%)	3,760 (83.0%)	0.02
Respiratory	486 (10.7%)	705 (12.1%)		486 (10.7%)	532 (11.7%)	
Drug overdose	112 (2.5%)	117 (2.0%)		112 (2.5%)	92 (2.0%)	
Other	137 (3.0%)	197 (3.4%)		137 (3.0%)	144 (3.2%)	
Received bystander CPR (n, %)	1,399 (30.9%)	1,679 (28.8%)	0.05	1,399 (30.9%)	1,317 (29.1%)	0.04
Initial shockable rhythm (n, %)	1,327 (29.3%)	1,504 (25.8%)	0.08	1,327 (29.3%)	1,144 (25.3%)	0.08
Received advanced airway placement (%)	3,825 (84.5%)	4,951 (85.0%)	0.01	3,825 (84.5%)	3,840 (84.8%)	0.01
EMS response time (minutes, ±SD)	7.80 (± 3.84)	7.72 (± 3.80)	0.02	7.80 (± 3.84)	7.76 (± 3.82)	0.01
PSAP call receipt to first epinephrine interval (minutes, ±SD)	16.45 (± 5.10)	16.17 (± 5.10)	0.05	16.45 (± 5.10)	16.23 (± 5.09)	0.04

ASD: Absolute Standardized Differences; CPR: Cardiopulmonary Resuscitation; EMS: Emergency Medical Services; PSAP: Public Safety Access Point; ROSC: Return of Spontaneous Circulation; SD: Standard Deviation.

Table 3. Adjusted odds ratios for ROSC.

	Complete Sample ($n = 10,350$)			Propensity Score Matched Sample ($n = 9,056$)		
Variable	Odds Ratio	95% CI	*p*-value	Odds Ratio	95% CI	*p*-value
First Epinephrine Route						
Intravenous		Reference			reference	
Intraosseous	0.770	0.710-0.835	<0.001	0.850	0.795-0.908	<0.001
Age (per year)	0.999	0.996-1.001	0.290	1.000	0.997-1.002	0.768
Male sex	0.725	0.666-0.788	<0.001	0.825	0.756-0.901	<0.001
Non-Caucasian	0.931	0.849-1.022	0.132	1.039	0.943-1.144	0.440
Etiology of Arrest						
Presumed cardiac	Reference			reference		
Respiratory	1.650	1.456-1.870	<0.001	1.434	1.265-1.626	<0.001
Drug overdose	1.535	1.164-2.024	0.002	1.237	0.937-1.633	0.134
Other	1.092	0.869-1.372	0.450	0.981	0.780-1.233	0.867
Received bystander CPR	1.124	1.029-1.228	0.010	1.057	0.964-1.158	0.236
Initial shockable rhythm	1.466	1.337-1.607	<0.001	1.247	1.134-1.372	<0.001
Received advanced airway placement	1.332	1.188-1.493	<0.001	1.239	1.098-1.397	<0.001
PSAP call receipt to first epinephrine interval	0.964	0.956-0.972	<0.001	0.976	0.968-0.984	<0.001

CPR: Cardiopulmonary Resuscitation; PSAP: Public Safety Access Point.

For each first epinephrine route, simple linear regression was used to fit a trend line to the proportion of patients with ROSC for each 1-min increment in call receipt-to-first epinephrine interval. Because the regression equations are not weighted by sample size and are therefore subject to the risk of bias from small sample sizes, all call receipt-to-first epinephrine categories with less than five patients were excluded from this analysis. The regression models indicated differing slope coefficients for ROSC between the IV and IO routes until convergence around 29 min post-arrest (Figure 2). From these regression equations, the call receipt-to-IV drug administration interval could be calculated to

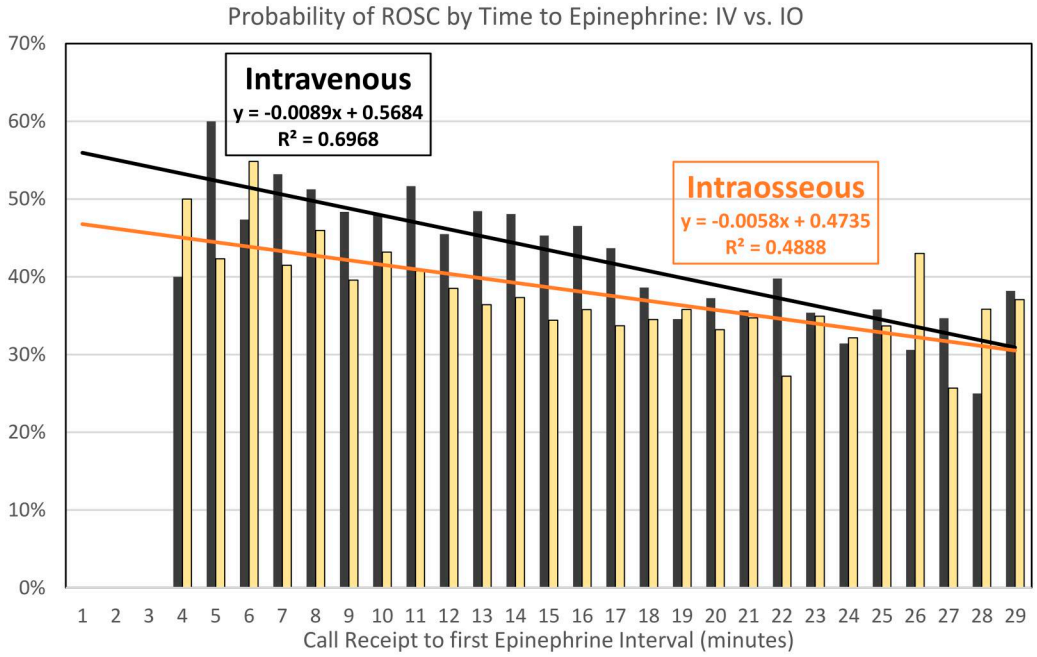

Figure 2. Probability of ROSC by Time to Epinephrine: IV vs. IO routes.

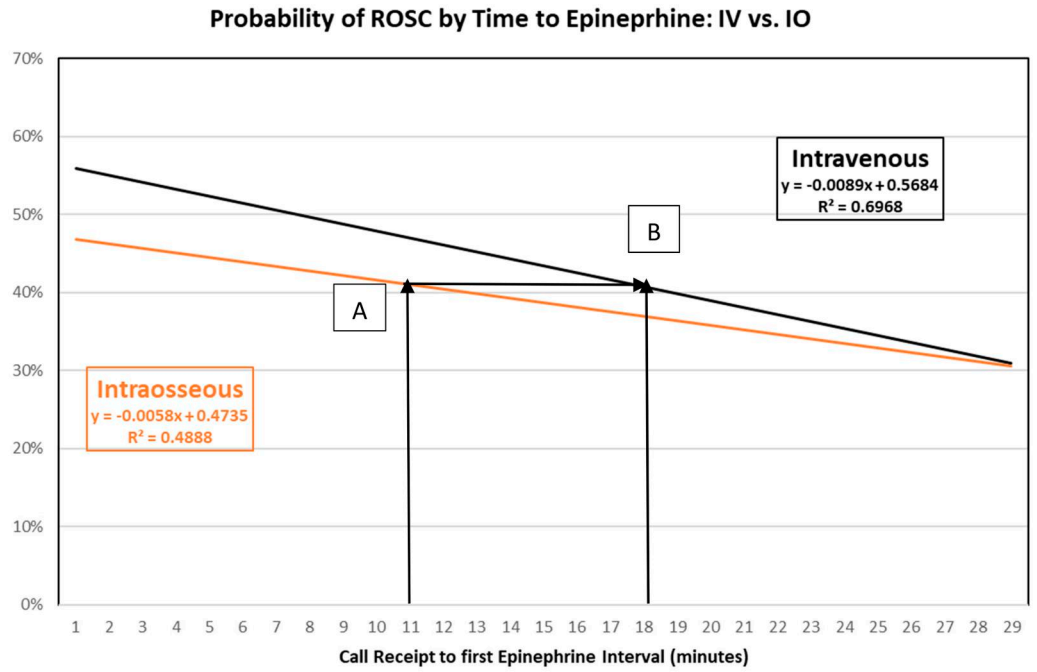

Figure 3. Calculation of call receipt to first epinephrine intervals with equivalent probabilities of ROSC between the IV and IO routes.

yield an equivalent predicted probability of ROSC for any call receipt-to-IO drug administration interval. Graphically, the length of a horizontal line originating from any time point on the IO trend line (e.g., Figure 3, point A) to its intersection with the IV trend line (e.g., Figure 3, point B), represents the additional time available that would yield a predicted probability of ROSC equivalent to that of the IO route if the epinephrine were administered IV. The additional time allowed to establish an IV and administer epinephrine intravenously for an equivalent predicted probability of ROSC declined linearly from 9 min at a call receipt-to-intraosseous epinephrine interval of 4 min to essentially no additional time at a call receipt-to-intraosseous epinephrine interval of 29 min at which the trend lines converged (Figure 4).

Discussion

To date, there has been no randomized controlled trial comparing first epinephrine administration routes in OHCA. Several observational studies appear in the literature but provide conflicting results. As well, many of these studies

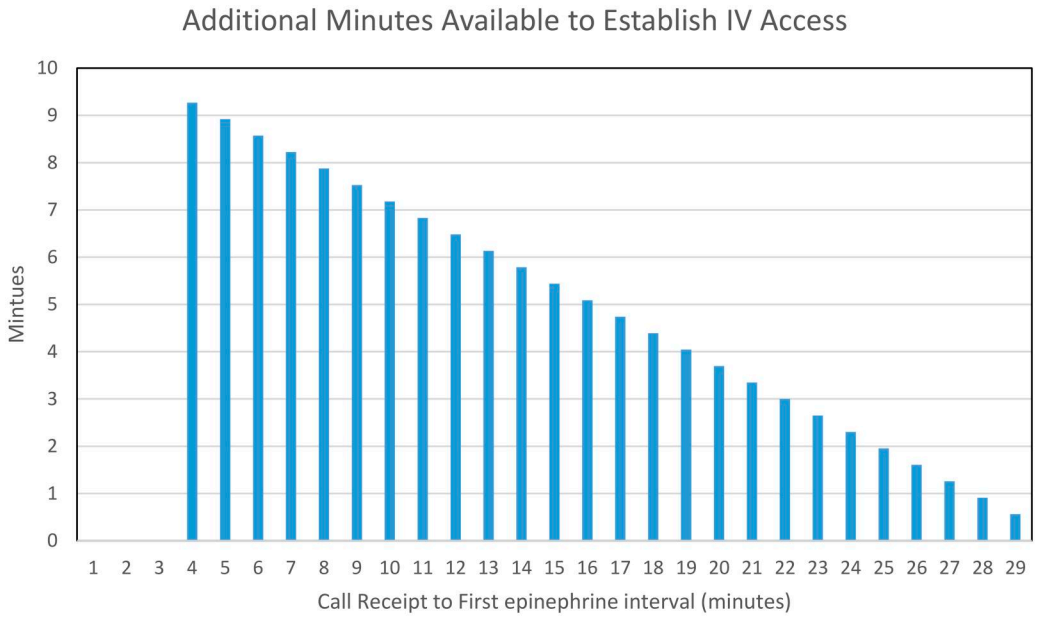

Figure 4. Additional minutes available for administering epinephrine intravenously with ROSC probabilities equivalent to the IO route.

did not control for the potential biases of indication or resuscitation time.

In a meta-analysis of observational studies by Morales-Cane et al, the pooled results revealed a lower likelihood of ROSC (OR = 0.69), survival to hospital discharge (OR = 0.65), and a statistically non-significant trend toward lower survival with favorable neurological outcome with intraosseous epinephrine (21). In a later meta-analysis, Grandfeldt et al reported that IO medication administration was associated not only with lower odds of ROSC (OR = 0.72) and survival to hospital discharge (OR = 0.71), but also with worsened neurological outcomes (OR = 0.60) (22). More recently, a meta-analysis by Hsieh et al offers conflicting evidence on the influence of epinephrine route (23). They reported worsened short-term survival when the IO route was used for medication administration (OR = 0.71), but non-significant trends for worsened survival to hospital discharge (OR = 0.66) and discharge with favorable neurological outcomes (OR = 0.60). More importantly, this study noted the need to adjust for the interval from collapse to drug administration, which was a significant outcome moderator.

In our retrospective analysis of a large EMS health records database, we found that the odds of prehospital ROSC were substantially lower when the first dose of epinephrine was administered intraosseously compared to patients receiving epinephrine intravenously. This association persisted in multivariable models, even after adjustment for the collapse time-to-drug administration interval and other potential confounders, as well as after propensity score matching. Our findings add to the growing body of evidence suggesting that IO as the first route for drug delivery is associated with lower odds of prehospital ROSC.

The presumed advantage of the IO route is that it provides faster and more reliable vascular access, and therefore, faster drug delivery, which is associated with an increased likelihood of ROSC. Although we didn't have data on prior missed IV access attempts, we observed a statistically significant, yet likely clinically insignificant, EMS scene arrival-to-drug delivery time advantage of the IO route compared to IV (8.04 vs. 8.25 min, $p = 0.007$). Our findings are similar to two prior investigations that found statistically significant but clinically meaningless differences favoring the IO route in scene arrival-to-vascular access intervals (19,24). However, this contrasts with other investigations that found drug delivery intervals to be 1-4 min faster *via* the IO route; although, some of these reported intervals included EMS response time, which obfuscates interpretation (11,16,25).

If we accept that IO is indeed faster but with worsened outcomes, the key clinical question becomes when to abandon further IV attempts in favor of obtaining IO access. We used the modeled linear trends from our dataset to calculate the call receipt-to-epinephrine intervals for the IO and IV routes that would provide equivalent, albeit unadjusted, probabilities of ROSC. This difference reflects the additional time beyond a hypothetical IO drug administration time during which an IV could be established and epinephrine administered with the same predicted probability of ROSC. Presumably, intravenous drug administration at any point prior to this time-based equivalency would result in a marginally higher likelihood of ROSC. In our sample, the mean call receipt-to-first epinephrine interval *via* the IO route was 16 min with a predicted probability of ROSC of 38.1%. From our regression equations, the call receipt-to-first epinephrine interval *via* the IV route that yielded the same probability of ROSC was 21 min. Thus, at this point in the resuscitation timeline, an additional 5 min would be available to establish an IV and administer the first bolus of epinephrine without any reduction in the probability of ROSC. More importantly, administering the drug intravenously in less than this 5-min allowance would provide a marginally higher probability of ROSC compared to the IO route.

The animal lab literature provides the physiological underpinnings for the hypothetical drug administration

intervals suggested by our findings. Intraosseous epinephrine, even when administered earlier, may be limited in its ability to provide tangible clinical benefits due to unfavorable pharmacokinetics. Previous animal models have demonstrated that intraosseous epinephrine has a lower maximum concentration (Cmax) and/or a longer time to maximum concentration (Tmax). In a systematic review, Hooper et al, reported on six studies of tibial IO vs. IV in normovolemic animal models (26). While study heterogeneity precluded a pooled analysis, they noted that the forest plots of Cmax and Tmax favored the IV route, although some of the confidence intervals transected zero. Notably, the reported IO Cmax values achieved only 17%-74% of the values of their IV counterparts, and the IO route took 1.4 − 2.5 times longer to reach Tmax. Due to the lower Cmax, some investigators have recommended larger doses when epinephrine is administered *via* the IO route (27,28). Additionally, the longer Tmax times reported for the IO route provide support for an additional, albeit finite, time window for establishing IV access as suggested by our findings.

Although nothing appears in the EMS OHCA literature with which to directly compare our findings, one animal study offers a single point of reference regarding the relationship between ROSC and the route and timing of epinephrine administration. In a swine model of prolonged arrest, Zuercher et al initiated CPR after 10 min of untreated ventricular fibrillation (29). At minute 11, one group of ten swine (early IO group) received 0.045 mg/kg of epinephrine intraosseously. A second group of ten received the same epinephrine dose intravenously at minute 18 (late IV group), and a third group of ten received placebo at minute 11 (placebo group). Defibrillation was attempted following every cycle of 200 compressions with epinephrine repeated as indicated. Survival at 24 h was greater in the early IO group compared to the late IV group (100% vs. 40%, $p = 0.01$), but there was no statistically significant difference in survival with favorable neurological outcome (60% vs. 30%, $p = 0.37$) or ROSC (10 of 10 vs. 9 of 10, $p = 1.0$), although the sample size was small and potentially underpowered. The authors concluded that early IO epinephrine resulted in shorter time to ROSC, reduced total defibrillation energy, and substantially better 24-h survival rate compared to delayed IV epinephrine. Although their conclusion contrasts with our findings, we found similarities between their epinephrine administration times and ROSC rates and those of our own. They found no statistically significant difference in the short-term outcome of ROSC between IO epinephrine administered at 11 min vs. IV epinephrine administered at 18 min. From our regression model, we too found nearly equivalent predicted ROSC rates for IO epinephrine at 11 min (41.0%) and for IV epinephrine at 18 min (40.8%). Although our retrospective study of human OHCA is not directly comparable to their laboratory experiment using an animal model of prolonged arrest, both studies point to a finite window of time during which IV epinephrine may show non-inferiority in attaining ROSC, even if administration is delayed beyond when it could have potentially been administered *via* the IO route.

Limitations

Limitations in our study design and data source warrant caution when interpreting our findings. Importantly, this study is subject to the customary limitations of retrospective design, including the completeness and accuracy of data reporting, as well as limiting our conclusions to those of association. In addition, such associations are limited to those patients consistent with our inclusion and exclusion criteria, which was witnessed, non-traumatic cardiac arrest prior to EMS arrival.

We did not investigate what proportion of patients in the IO group experienced failed IV attempts prior to IO drug administration and vice versa. It is possible that some patients received one intervention as a consequence of one or more failed attempts at the other intervention. However, our analysis was based on the actual timing of epinephrine administration irrespective of prior failed attempts at vascular access, and our findings should be interpreted through that lens. In addition, a small increase in the odds of ROSC has been reported when epinephrine is delivered *via* an upper extremity IO site compared to a lower extremity IO site (30). We did not control for the anatomical location of the IO or IV sites used for epinephrine delivery, and this may have influenced our results.

As best as possible, we attempted to control for the biases of indication and resuscitation time by limiting our sample to witnessed arrests as well as using statistical adjustment *via* multivariate modeling and propensity score matching. In contrast, our calculations of IO and IV call receipt-to-drug administration ROSC probabilities were derived from simple linear regression models and are therefore unadjusted. We consider these estimates to be imprecise approximations necessitating validation in follow-up studies.

Our data were collected during the COVID-19 pandemic, which is associated with increased cases of OHCA with worsened outcomes, overall lower rates of resuscitation, and coagulopathies leading to OHCA (31,32). Nonetheless, our observed ROSC rates remained relatively high. We suspect this may be due to our inclusion criteria, which limited our sample to witnessed arrests. As well, our sample had a modestly higher proportion of shockable presenting rhythms and shorter EMS response times in comparison to an analysis of the Cardiac Arrest Registry to Enhance Survival (CARES) data examining the impact of the COVID pandemic on OHCA resuscitation (33). Nonetheless, we lacked pre-pandemic data for our study sites and cannot definitively state how the pandemic may have influenced our results.

Finally, hospital discharge data as well as the timing and duration of ROSC for included patients were not universally available and the influence of first epinephrine administration route on longer-term outcomes remains unknown. However, we believe that early ROSC is an essential first step toward neurological recovery. As such, our findings should encourage further study into the coetaneous relationships among the timing of epinephrine, first drug delivery route, early ROSC, and neurological salvage.

Conclusions

Within the limitations of our methodology, we found that IO epinephrine was associated with lower odds of ROSC when adequate controls were in place for the timing of administration. When the drug is administered at the same time, *ceteris paribus*, the IV route demonstrates a better short-term outcome of ROSC. We further found that the superiority of the intravenous route in attaining ROSC persisted for several minutes beyond the time at which the drug could have been given intraosseously. Thus, there appears to be a finite window of opportunity in which intravenous epinephrine remains superior even if there are short delays in drug delivery. These findings suggest that the IV route should be the preferred and first attempted route of epinephrine delivery, with IO reserved as a rescue route when IV access is not successful. Additional prospective study is necessary to confirm these results and to establish if such a relationship persists across longer-term outcome measures. Such studies should also adequately address the threats of intention and resuscitation time bias.

Authors' Contributions

All authors contributed to the study conception, design, and implementation. Statistical analyses were performed by MH. The first draft of the manuscript was written by MH and all authors participated in the editing of the manuscript and approved the final draft for submission.

Declaration of Generative AI in Scientific Writing

The authors did not use a generative artificial intelligence (AI) tool or service to assist with preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

Disclosure Statement

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