Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Impact of adrenaline dose and timing on out-of-hospital cardiac arrest survival and neurological outcomes

Adam P. Sigal[a,*], *Kristen M. Sandel*[a], *David G. Buckler*[b], *Thomas Wasser*[c], *Benjamin S. Abella*[b]

[a] Department of Emergency Medicine, Reading Hospital, West Reading, PA, United States
[b] Center for Resuscitation Science and the Department of Emergency Medicine, University of Pennsylvania, Philadelphia, PA, United States
[c] Consult-Stat: Complete Statistical Services, Macungie, PA, United States

Abstract

Study Objective: The 2015 ILCOR Advanced Cardiovascular Life Support Guidelines recommend intravenous adrenaline (epinephrine) as a crucial pharmacologic treatment during cardiac arrest resuscitation. Some recent observational studies and clinical trials have questioned the efficacy of its use and suggested possible deleterious effects on overall survival and long-term outcomes. This study aimed to describe the association between time and dose of adrenaline on return of spontaneous circulation (ROSC) and neurologic function.

Methods: We performed a retrospective analysis of the Penn Alliance for Therapeutic Hypothermia (PATH) data registry. The timing of the first dose of adrenaline and the total dose of adrenaline during cardiac arrests was compared between survivors to discharge and non-survivors for arrests lasting greater than 10 min.

Results: The registry contained 5594 patients. After excluding patients with an in-hospital cardiac arrest, a non-shockable rhythm, or no adrenaline administration, 1826 were included in the final analysis. Survivors to discharge received adrenaline sooner (median 5.0 vs. 7.0 min, $p = 0.022$) and required a lower total dose than non-survivors (2.0 vs. 3.0 mg, $p < 0.001$). For survivors, there was no significant association between the time to first adrenaline dose and favorable neurological outcome as measured by Cerebral Performance Category (CPC). Among survivors, those that received less than 2 mg of adrenaline had a more favorable neurologic outcome than those administered > 3 mg. (CPC 1–2 16.6% vs. 12.5%, $p = 0.004$).

Conclusion: Early adrenaline administration is associated with a higher percentage of survival to discharge but not associated with favorable neurological outcome. Those patients with a favorable neurologic outcome received a lower total adrenaline dose prior to ROSC.

Keywords: Adrenaline, Epinephrine, Cardiac arrest, Survival, Neurological outcomes, OHCA, ACLS

Introduction

Over 350,000 people suffer an out-of-hospital cardiac arrest (OHCA) in the United States each year. Emergency Medical Services (EMS) personnel treated approximately 60% of these cases. In 2015, only 10.6% survived to hospital discharge and 8.56% survived with good neurological function. For a witnessed OHCA with an initial shockable rhythm, survival and neurologic recovery were 33.6% and 30.1%, respectively.[1]

Intravenous adrenaline (epinephrine) administration remains an integral part of the Advanced Cardiovascular Life Support (ACLS) guidelines.[2] Recent studies have raised concerns about the efficacy and possible deleterious effects of adrenaline on both overall survival and long-term neurological outcome.[3,4] Other studies suggest that the timing of adrenaline administration may

* Corresponding author at: The Reading Hospital, PO Box 16052, Reading, PA 19612, United States.
E-mail address: adam.sigal@towerhealth.org (A.P. Sigal).

https://doi.org/10.1016/j.resuscitation.2019.04.018
Received 12 October 2018; Received in revised form 7 March 2019; Accepted 4 April 2019

influence survival.[5] Results from the PARAMEDIC2 trial, a randomized double-blind trial in the United Kingdom, showed that adrenaline resulted in a significantly higher 30-day survival compared to placebo but did not result in a favorable rate of neurologic outcome.[6] Addressing these complex data, investigators have suggested that the clinical effects of adrenaline likely hinge on timing and dosing; limited work has been performed in the US to assess these factors among OHCA patients. There is a need to determine if there are a subset of patients who benefit from adrenaline, as some patients do achieve return of spontaneous circulation (ROSC) with adrenaline administration.[7] In this study, we analyze the association between timing of adrenaline administration as well as the total dose of adrenaline given on survival and neurologic functional outcomes in a well-established multicenter cohort of OHCA patients. We hypothesize that early adrenaline administration in OHCA is associated with greater survival and neurologic function.

Methods

We performed a retrospective observational study utilizing data from the Penn Alliance for Therapeutic Hypothermia (PATH) database, an internet-based cardiac arrest and post-arrest care registry hosted at the University of Pennsylvania. The PATH registry has previously been described and has been used for analysis of OHCA outcomes.[8] Member hospitals submit case data for all cardiac arrests events, both OHCA and IHCA, where resuscitation was attempted by the hospital, including demographic, arrest event and outcome variables. To date, 34 institutions have submitted cardiac arrest cases to the registry. All participating institutions contribute at minimum a data set comprised of about 30 variables. A subset of institutions enters a more extensive research data set comprised of 100 data points, including detailed intervention data including intervention timing, serial lab results, and post-arrest patient body temperatures. Due to different participation levels, some data are not collected for all patients. To ensure data quality, the PATH database manager reviews a random sample of 15% of cases submitted from all institutions. Periodic reviews of the reported case frequency are conducted to identify possible gaps in reporting. Data quality errors and reporting inconsistencies are flagged for review by the submitting institution. The current analysis from the PATH registry was approved by the University of Pennsylvania Institutional Review Board and the Reading Hospital Institutional Review Board.

We analyzed data on OHCA patients with at least 10 min of resuscitative efforts, defined by the interval from arrest onset to ROSC or termination of resuscitation efforts. The rationale for this was that OHCA with return of spontaneous circulation (ROSC) after shorter resuscitations often have a shockable rhythm that responds to early defibrillation alone without the establishment of intravenous access and adrenaline dosing, which would skew the analysis. We used the arrest event duration of at least 10 min cutoff assuming these patients would have had the opportunity to receive at least one dose of adrenaline. In addition to analyzing the association between adrenaline timing and dosing on survival, we also reviewed the association between timing and dosing on neurologic function of survivors as defined by the Cerebral Performance Category (CPC) of arrest events lasting at least 10 min. The timing intervals were similar to those used in prior studies.[9,10]

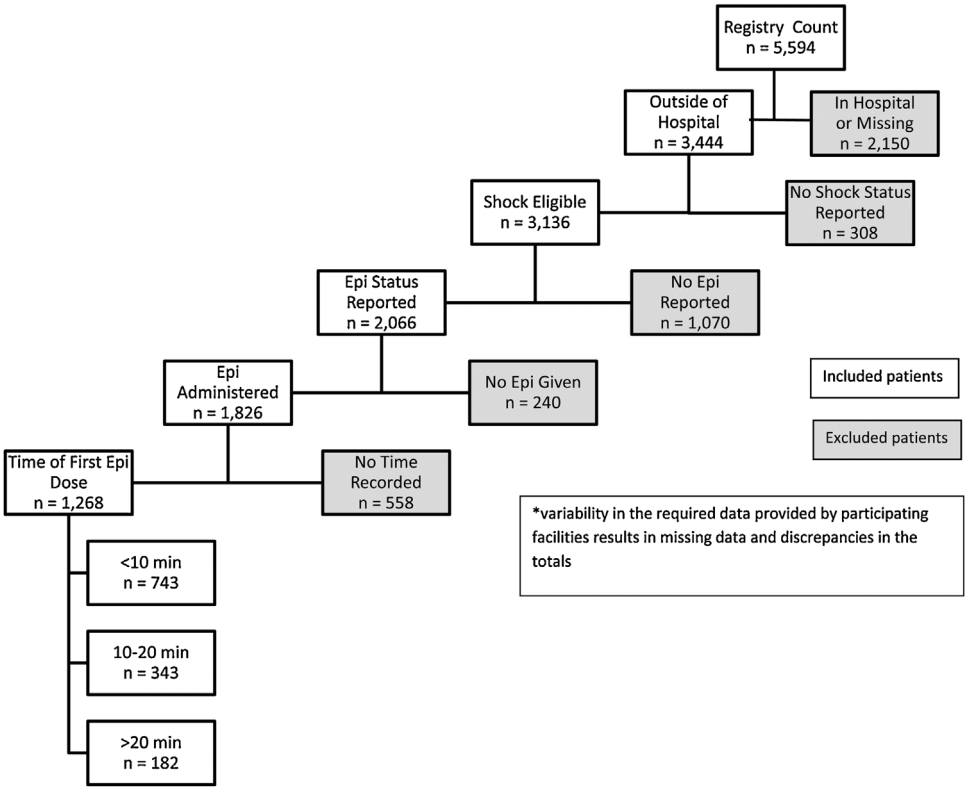

Fig. 1 – Registry data and inclusion in final analysis. Study included only out-of-hospital cardiac arrest patients who were shock eligible and had epinephrine administered.

All statistical analysis was performed using standard software (SPSS v25, IBM Corp, Armonk, New York, USA). Descriptive statistics were reported as count and percent within category. Continuous data were reported as mean ± Standard Deviation (SD), in addition where there were outliers in the data, the median value was reported as well. Analysis of categorical variables was performed by Chi-square test of association. Continuous variables were analyzed by group t-test. A p-value of 0.05 ($p < 0.05$) was considered statistically significant. Due to the exploratory nature of this study and to not miss individual variable contribution to survival there were no corrections applied to the data for multiple comparisons.

Results

The PATH registry at the time of the analysis contained arrest data from 5594 patients, of those 3136 were OHCA with a shockable rhythm; 1268 patients received intra-arrest adrenaline with timing documented and were included in the final analysis (Fig. 1 Table 1). There were no significant differences in the percentage of males and females (59.4% vs 58.1% males and 40.6% vs 41.9% females P = 0.757) that had no adrenaline vs adrenaline administered (Table 2). The majority had known coronary disease or risk factors for coronary disease. In addition, 64% of patients had a witnessed arrest and the overall survival rate for the 1541 with complete data recorded was 17.5% (Table 3).

2066 patients received adrenaline during resuscitation efforts. Data on the dose of adrenaline and the timing of first dose were only available on 1826 and 1268 patients, respectively. We limited our analysis to patients whose resuscitation lasted longer than 10 min. Final analysis on the timing of first dose and total dose, therefore, was performed on 431 and 538 patients, respectively (Fig. 1 and Table 5)

Duration of resuscitative efforts for non-survivors was significantly longer than survivors (median time 27 min, SD 27.63 vs 20 min, SD 19.3, $p < 0.001$ IQR 24 vs 14) (Table 5). For those with resuscitations efforts lasting at least 10 min, survivors requiring adrenaline received the first dose significantly earlier than those that died (5 min SD 10.06 vs 7 min, SD 14.74, $p < 0.022$, IQR 8.5 vs 12). Survivors also received a significantly lower dose of adrenaline to achieve ROSC than those that died (median 2.0, SD 1.65, vs 3.0, SD 2.40, $p < 0.001$, IQR 2 vs 3) (Table 5).

In addition, for resuscitations lasting greater than 10 min, there was no significant difference in neurologic outcome regardless of time to first dose of adrenaline or the total dose administered. However, for survivors, those that received less than 2 mg of adrenaline had a more favorable neurologic outcome than those administered > 3 mg. (CPC 1–2 16.6% vs. 12.5%, p = 0.004). (Table 6).

A greater percentage of those patients with ROSC that did not require epinephrine received therapeutic hypothermia and PCI than in the Epinephrine cohort. However, few of the survivors had timing of epinephrine recorded in the Registry limiting analysis on the influence of post resuscitative **care on** outcome (Table 4).

Discussion

In this retrospective multicenter evaluation of OHCA events, earlier administration of adrenaline was associated with ROSC for those resuscitations lasting at least 10 min. This is consistent with

Table 1 – Demographics and comorbid counts for Study eligible patient cohort (5286). Table does not include counts for patients in the registry with missing values so counts will not sum to 3255 for all variables.

Variable	Category	Shock eligible (n = 3255)	
		Count	Percent
Gender	Female	1224	37.6
	Male	2030	62.4
Race	White	1804	55.5
	Black	1014	31.2
	Hispanic	82	2.5
	Asian/Pacific Islander	29	0.9
	Other	35	1.1
	Unknown	289	8.9
	None	2	0.01
Arrhythmia	Atrial Fib/Flutter	160	87.0
	Bradycardia	9	4.9
	Supraventricular tack	6	3.3
	Ventricular tach	9	4.9
Asthma	No	3138	96.4
	Yes	117	3.6
Prior CHF	No	2933	90.1
	Yes	322	9.9
Coronary srtery disease	No	2877	88.4
	Yes	378	11.6
Deep vein thrombosis	No	3194	98.1
	Yes	61	1.9
Diabetes mellitus	No	2712	83.3
	Yes	543	16.7
Hypertension	No	2295	70.5
	Yes	960	29.5
Implanted defibrillator	No	3235	99.4
	Yes	20	0.6
Vena cava filter	No	3252	99.9
	Yes	3	0.1
Morbid obesity	No	3136	96.3
	Yes	119	3.7
Myocardial ischemia prior to event	No	3096	95.1
	Yes	159	4.9
Myocardial ischemia during event	No	3192	98.1
	Yes	63	1.9
Hypoventilation	No	3247	99.8
	Yes	8	0.2
Pacemaker	No	3209	98.6
	Yes	46	1.4
Peripheral vascular disease	No	3157	97.0
	Yes	98	3.0
Pulmonary embolism	No	3224	99.0
	Yes	31	1.0
Renal insufficiency	No	3075	94.5
	Yes	180	5.5
Respiratory insufficiency	No	3230	99.2
	Yes	25	0.8
Event witnessed	No	1114	36.0
	Yes	1981	64.0
Endotracheal trach tube	No	7	5.1
	Yes	131	94.9
PCI performed	No	6	4.2
	Yes	138	95.8
Recoded time to first epinephrine	<10 min	405	44.9
	10–20 min	323	35.8
	>20 min	174	19.3
Mortality	Dead	2702	83.1
	Alive	551	16.9

the suggestion by Hansen that the timing and dose of adrenaline are important confounders of the survival benefit of adrenaline during resuscitation.[11] However, timing of the first dose was not associated with improved neurologic outcome, although those survivors with favorable outcome received lower doses of adrenaline.

Adrenaline's role in improving ROSC may be in its alpha-agonist effect by improving coronary perfusion and aortic diastolic pressures. However, its beta-agonist effects of increasing myocardial work, promoting dysrhythmias, as well as its effects on platelet activation and clot formation, may have adverse effects on neurologic injury and recovery. These conflicting alpha and beta agonist effects may

Table 2 – Demographics and comorbid goodness of fit testing between the Epi Administered and No Epi Given cohorts. Test is Chi-square.

Variable	Category	No-Epi administered (n = 165)		Epi administered (n = 1376)		p-value
		Count	Percent	Count	Percent	
Gender	Female	67	40.6	576	41.9	0.757
	Male	98	59.4	800	58.1	
Race	White	83	50.3	468	34.0	<0.001
	Black	55	33.3	812	59.1	
	Hispanic	1	0.6	21	1.5	
	Asian/Pacific Islander	6	3.6	18	1.3	
	Other	3	1.8	17	1.2	
	Unknown	17	10.3	39	2.8	
	None	0	0.0	1	0.01	
Arrhythmia	Atrial Fib/Flutter	17	73.9	95	88.8	0.294
	Bradycardia	3	13.0	5	4.7	
	Supraventricular tack	1	4.3	2	1.9	
	Ventricular tach	2	8.7	5	4.7	
Prior CHF	No	138	83.6	1152	83.7	0.978
	Yes	27	16.4	224	16.3	
Coronary artery disease	No	115	69.7	1131	82.2	<0.001
	Yes	50	30.3	245	17.8	
Deep vein thrombosis	No	159	96.4	1334	96.9	0.683
	Yes	6	3.6	42	3.1	
Diabetes mellitus	No	119	72.1	982	71.4	0.839
	Yes	46	27.6	394	28.6	
Hypertension	No	81	49.1	681	49.5	0.923
	Yes	84	50.9	695	50.5	
Implanted defibrillator	No	161	97.6	1367	99.3	0.019
	Yes	4	2.4	9	0.7	
Myocardial ischemia prior to event	No	144	87.3	1271	92.4	0.024
	Yes	21	12.7	105	7.6	
Myocardial ischemia during event	No	156	94.5	1348	98.0	0.007
	Yes	9	5.5	28	2.0	
Hypoventilation	No	164	99.4	1373	99.8	0.355
	Yes	1	0.6	3	0.2	
Pacemaker	No	164	99.4	1341	97.5	0.119
	Yes	1	0.6	35	2.5	
Peripheral vascular disease	No	158	95.8	1325	96.3	0.732
	Yes	7	4.2	51	3.7	
Pulmonary embolism	No	162	98.2	1357	98.6	0.655
	Yes	3	1.8	19	1.4	
Respiratory insufficiency	No	165	100.0	1362	99.0	0.193
	Yes	0	0.0	14	1.0	
Event witnessed	No	26	16.5	561	42.9	<0.001
	Yes	132	83.5	748	57.1	
Endotracheal trach tube	No	0	0	7	5.1	n/a
	Yes	0	0	131	94.9	
PCI performed	No	1	5.3	2	4.7	0.918
	Yes	18	94.7	41	95.3	
Recoded time to first epinephrine	<10 min			405	44.9	n/a
	10–20 min			323	35.8	
	>20 min			174	19.3	
Mortality	Dead	59	35.8	1,213	88.2	<0.001
	Alive	106	64.2	163	11.8	

Table 3 – Post resuscitation care of patient patients with ROSC on Emergency Department arrival.

Variable	Category	No-Epi administered (n = 165)		Epi administered (n = 1376)		p-value
		Count	Percent	Count	Percent	
Event witnessed	No	26	16.5	561	42.9	<0.001
	Yes	132	83.5	748	57.1	
Endotracheal trach tube	No	0	0	7	5.1	n/a
	Yes	0	0	131	94.9	
PCI performed	No	1	5.3	2	4.7	0.918
	Yes	18	94.7	41	95.3	
Recoded time to first epinephrine	<10 min			405	44.9	n/a
	10–20 min			323	35.8	
	>20 min			174	19.3	
Mortality	Dead	59	35.8	1213	88.2	<0.001
	Alive	106	64.2	163	11.8	

Table 4 – Post resuscitative care for patients who obtained ROSC and EPI times recorded. Note PCI count for patients in the Epi cohort are different than noted in Table 3 as timing of Epinephrine was not recorded for all patients in the Registry.

Time interval	Epi		No Epi	
	Cooling count (%)	PCI count (%)	Cooling count (%)	PCI count (%)
<10 min	37 (45.7)	5 (55.6)	77 (66.4)	18 (100%)
10–20 min	34 (42.0)	3 (33.3)		
20+ min	10 (12.3)	1 (11.1)		

account for the initial improvement in ROSC but not the improvement in hospital survival or neurologic function compared to those resuscitations without adrenaline use.[7] For OHCA lasting greater than 10 min, adrenaline appears to have a survival benefit if administered early during the resuscitation. Early administration and dosing, however, does not appear to result in functional improvement. There have been contradictory studies on the use of pre-hospital adrenaline, even from studies that have analyzed the same registries, secondary to different analytical methods. An initial review of All-Japan Registry of OHCA patients concluded that earlier adrenaline administration may be associated with higher rates of all survival and survival with favorable neurologic function.[5] Hagihara and Nakahara analyzed the same registry using different time periods. Although the earlier study did not adjust for timing of adrenaline, both demonstrated the increase in ROSC but not in long term survival or functional outcome.[12,13] These studies were also limited in not accounting for post-resuscitative care that may have impacted survival. A recent secondary analysis of OHCA from the Resuscitation Outcomes Consortium (ROC) also found an association between survival and the timing or adrenaline with those receiving the first dose in less than 10 min having a higher rate of survival compared to those receiving adrenaline after 10 min.[11] This time dependent outcome to survival was also observed in a review of OHCA in Arizona.[14] In contrast to the SHARE data base review, the ROC analysis suggests that earlier administration also improves neurologic outcome. A recent retrospective study of the Get With The Guidelines-Resuscitation registry showed that for in-hospital cardiac arrests, very early administration of adrenaline was associated with a decreased odds of ROSC, hospital discharge and good neurologic function.[15] Early administration was defined as within 2 min of the first defibrillation. This time interval is rarely achieved from the start of resuscitative efforts in OHCA. In addition, the time interval from arrest to first dose can be difficult to calculate.

In addition, prospective randomized clinical trials have failed to demonstrate a survival benefit. Olasveengen et al. demonstrated in a trial of OHCA patients randomized to either Advanced Cardiac Life Support with access to intravenous (IV) medications or ACLS without intravenous medication that the IV access group did have a statistical improvement in ROSC compared to those with no IV access medication (40% vs 25%, OR, 1.99; 95% CI, 1.48–2.67; $P < .001$). However there was no significant improvement in survival to hospital discharge (10.5% vs 9.2%, OR, 1.16; 95% CI, 0.74–1.82; $P = 0.61$) or neurological outcome (9.8% vs 8.1%, OR, 1.24; 95% CI, 0.77–1.98; $P = 0.45$).[16] A post-hoc analysis of the data set for those that actually received adrenaline compared to those that did not again supported that adrenaline is associated with short term survival but not with actual survival to hospital discharge and survival with favorable neurologic outcomes.[17] Jacobs et al.

Table 5 – Continuous analysis (Group t-test) Mortality against Time to first Epinephrine dose and total epinephrine dose for resuscitations lasting > = 10 min.

Variable	Dead					Alive					p-value
	n	Mean	Median	SD	IQR	n	Mean	Median	SD	IQR	
Time to first Epi	313	10.79	7.0	14.7	12	118	7.92	5.0	10.06	8.5	0.022
Epi-dose	395	3.93	3.0	2.40	3	143	2.70	2.0	1.65	2	<0.001
Code duration	1135	33.60	27.0	27.63	24	328	24.73	20.0	19.30	14	<0.001

Table 6 – Chi-square analysis in the recoded CPC variable in the surviving patients for resuscitations lasting > = 10 min.

Variable	Category	CPC 1–2		CPC 3–5		p-value
		Count	%	Count	%	
Recoded time to first EPI	<10	63	68.5	199	63.0	0.353
	10–20	22	23.9	76	24.1	
	>20	7	7.6	41	13.0	
Recoded Epi dose	1–2	59	16.6	146	12.5	0.004
	3–4	38	10.7	135	11.5	
	5–6	7	2.0	73	6.2	
	7+	252	70.8	817	69.8	

demonstrated similar results in their double blind randomized placebo-controlled trial of adrenaline in OHCA. The adrenaline group had a significant increase in ROSC compared to the placebo group (23.5% vs 8.4%, OR 3.4; 95% CI 2.0–5.6) but no significant improvement in patients surviving to hospital discharge (4.0% vs 1.9%, OR 2.2; 95% CI 0.7–6.3%).[18] Although this was a well-designed study, it was significantly underpowered based on their a priori calculations because of patient recruitment complications. Most recently, the PARAMEDIC2 investigation, a randomized, controlled, double-blinded trial, demonstrated a significant higher 30-day survival with adrenaline use compared to placebo but no benefit in survival to hospital discharge or neurological outcome.[6] The percent of survivors receiving either adrenaline or placebo in this study (3.2% and 2.4% respectively) was much lower than the 17.5% overall survival observed in our registry.

As predicted, those with ROSC had shorter duration of resuscitation. The chance of ROSC decreases with duration of asystole, pulseless electrical activity or pulseless ventricular rhythm. Those OHCA due to ventricular fibrillation or pulseless ventricular tachycardia might respond to early defibrillation and never have time for adrenaline administration. Prolonged resuscitative efforts allow more opportunities for repeat doses of adrenaline. The continued administration of adrenaline does not improve either survival or functional neurologic status.

This study has several limitations. This is a retrospective study performed on registry data. Not all participants in the registry were required to complete the same number of data elements so we did not have complete information on all the patients entered into the registry dataset. We are only able to comment on potential associations between the timing and total dose of adrenaline and survival with functional neurologic outcome, causation is not assumed, and it is likely that other unstudied confounders may have impacted these findings.

Conclusions

The role of adrenaline in cardiac arrest resuscitation care remains complex. Our data support prior studies that suggest the benefit of adrenaline is maximized if given early during resuscitation efforts. Although it is associated with high rates of ROSC, in our data adrenaline use was only associated with improved neurological outcome if the total dose required is less than 2 mg. Further prospective studies are needed to determine the exact timing and dose benefit of adrenaline.

Conflicts of interest

Dr. Abella reports funding from the NIH, PCORI, Stryker Medical and the Medtronic Foundation. He has received honoraria and other educational funding from CR Bard, and serves as a volunteer with the American Heart Association.

None of the other authors declare any conflict of interests.

Acknowledgements

The authors would like to thank the member institutions of the Penn Alliance for Therapeutic Hypothermia registry. Without the data they provided for research and quality improvement, this project would not have been possible.

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146–603.
2. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S444–64.
3. Ong ME, Tan EH, Ng FS, et al. Survival outcomes with the introduction of intravenous adrenaline in the management of out-of-hospital cardiac arrest. Ann Emerg Med 2007;50:635–42.
4. Mayor S. Prehospital use of adrenaline reduces survival in cardiac arrest, study finds. BMJ 2014;349:g7430.
5. Nakahara S, Tomio J, Nishida M, Morimura N, Ichikawa M, Sakamoto T. Association between timing of adrenaline administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. Acad Emerg Med 2012;19:782–92.
6. Perkins GD, Ji C, Deakin CD, et al. A Randomized Trial of Adrenaline in Out-of-Hospital Cardiac Arrest. NEJM 2018;379:711–21.
7. Callaway CW. Questioning the Use of Adrenaline to Treat Cardiac Arrest. JAMA 2012;307:1198–200.
8. Perman SM, Grossestreuer AV, Wiebe DJ, Carr BG, Abella BS, Gaieski DF. The Utility of Therapeutic Hypothermia for Post-Cardiac Arrest Syndrome Patients With an Initial Nonshockable Rhythm. Circulation 2015;132:2146–51.
9. Hayashi Y, Iwami T, Kitamura T, et al. Impact of early intravenous adrenaline administration on outcomes following out-of-hospital cardiac arrest. Circ J 2012;76:1639–45.
10. Koscik C, Pinawin A, McGovern H, et al. Rapid adrenaline administration improves early outcomes in out-of-hospital cardiac arrest. Resuscitation 2013;84:915–20.
11. Hansen M, Schmicker RH, Newgard CD, et al. Time to Adrenaline Administration and Survival from Non-Shockable Out-of-Hospital Cardiac Arrest Among Children and Adults. Circulation 2018;137:2032–40.
12. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (adrenaline) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. BMJ 2013;347:f6829.
13. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata T, Miyazaki S. Prehospital adrenaline use and survival among patients with out-of-hospital cardiac arrest. JAMA 2012;307:1161–8.
14. Ewy GA, Bobrow BJ, Chikani V, et al. The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest. Resuscitation 2015;96:180–5.

15. Andersen LW. Early adminstration of adrenaline (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: prpensity score matched analysis. BMJ 2016;353:1577–99.
16. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA 2009;302:2222–9.
17. Olasveengen TM, Wik L, Sunde K, Steen PA. Outcome when adrenaline (adrenaline) was actually given vs. not given - post hoc analysis of a randomized clinical trial. Resuscitation 2012;83:327–32.
18. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138–43.