Original Research

Journal of Intensive Care Medicine
2021, Vol. 36(4) 459-465

DOI: 10.1177/0885066620906802
journals.sagepub.com/home/jic
SAGE

Pupillary Light Reflex Is Not Abolished by Epinephrine and Atropine Given During Advanced Cardiac Life Support in Patients Who Achieve Return of Spontaneous Circulation

Natalie Achamallah, MD, MA, MS[1,2], Jeffrey Fried, MD[1,3], Rebecca Love, RN, BSN, CCRN[1], Yuri Matusov, MD[1,2], and Rohit Sharma, MD[1]

Abstract

Introduction: Absence of pupillary light reflex (PLR) is a well-studied indicator of poor neurologic recovery after cardiac arrest. Interpretation of absent PLR is difficult in patients with hypothermia or hypotension, or who have electrolyte or acid-base disturbances. Additionally, many studies exclude patients who receive epinephrine or atropine from their analysis on the basis that these drugs are thought to abolish the PLR. This observational cohort study assessed for presence or absence of PLR in in-hospital cardiac arrest patients who received epinephrine with or without atropine during advanced cardiac life support and achieved return of spontaneous circulation (ROSC). **Methods:** Pupil size and reactivity were assessed in adult patients who had an in-hospital cardiac arrest, received epinephrine with or without atropine, and achieved ROSC. Measurements were taken using a NeurOptics NPi-200 infrared pupillometer. **Results:** Forty patients had pupillometry performed within 1 hour (median: 6 minutes) after ROSC. Of these only 1 (2.5%) patient had nonreactive pupils at first measurement after ROSC. The remaining 39 (97.5%) had reactive pupils. Of the 19 patients who had pupils checked within 3 minutes of ROSC, 100% had reactive pupils. Degree of pupil responsiveness was not correlated with cumulative dose of epinephrine. Ten patients received atropine in addition to epinephrine, including the sole patient with nonreactive pupils. The remaining 9 (90%) had reactive pupils.
Conclusion: Epinephrine and atropine do not abolish the PLR in patients who achieve ROSC after in-hospital cardiac arrest. Lack of pupillary response in the post-arrest patient should not be attributed to these drugs.

Keywords

cardiac arrest, pupillometry, prognostication, epinephrine

Introduction

Prediction of neurological recovery in post-cardiac arrest patients who do not immediately awaken can be a difficult task. In response to this challenge, Levy et al delineated an algorithm in which sequential examinations are correlated with the degree of expected impairment; the earliest metric measured in this algorithm is the presence or absence of pupillary light reflex (PLR) at first examination following return of spontaneous circulation (ROSC).[1]

Since the Levy paper in 1985 several groups have validated the absence of PLR as an indicator of poor prognosis.[2-4] Many, however, caution against potential confounders in the immediate post-arrest period including electrolyte, acid-base and endocrine disturbances, hypotension, hypothermia, and medications administered as part of resuscitative efforts. Patients who receive "confounding medications" such as epinephrine or atropine are frequently excluded from analysis despite lack of evidence to suggest that either interferes with PLR when administered systemically.[3-7]

Pupil dilatation and constriction are mediated by interplay between the sympathetic and parasympathetic autonomic

[1] Santa Barbara Cottage Hospital, Santa Barbara, CA, USA
[2] Cedars Sinai Medical Center, Los Angeles, CA, USA
[3] Keck School of Medicine University of Southern California, Los Angeles, CA, USA

Received October 05, 2019. Received revised January 22, 2020. Accepted January 27, 2020.

Corresponding Author:
Natalie Achamallah, Department of Medical Education, Santa Barbara Cottage Hospital, 400 W Pueblo Street, Santa Barbara, CA 93105, USA.
Email: natalie.achamallah@gmail.com

nervous systems. Topical application of sympathomimetic drugs directly stimulates *musculus dilator pupillae*, which dilates the pupil, and topical parasympatholytic drugs cause mydriasis and abolish the light reflex.[8] Medications such as epinephrine, which simulate sympathetic stimulation, and medications that block parasympathetic stimulation, such as atropine, are integral components of advanced cardiovascular life support (ACLS). Whether epinephrine and atropine inhibit the PLR when given systemically has significant clinical implications. Although speculation abounds in the literature, this question remains relatively poorly studied.[3-5,9]

This study aimed to evaluate whether administration of epinephrine or atropine abolished PLR in patients who underwent ACLS for in-hospital cardiac arrest and achieved ROSC.

Methods

After institutional review board approval, we conducted a prospective clinical study of in-hospital cardiac arrest occurring between September 2017 and February 2019 at Santa Barbara Cottage Hospital (SBCH). Santa Barbara Cottage Hospital is a community teaching hospital and regional referral center in Santa Barbara, California.

Adult patients who had an in-hospital cardiac arrest, underwent ACLS with administration of epinephrine with or without atropine, and achieved ROSC were considered eligible for inclusion. This included patients who arrested in the medical and surgical intensive care units (ICUs) or medical and surgical inpatient floors but not patients in the emergency department or operating room. Patients younger than the age of 18, patients who did not achieve ROSC, patients who did not receive epinephrine, and patients with known ophthalmologic history such as cataract surgery or coloboma were excluded.

In patients who achieved ROSC, pupil reactivity was assessed using a NeurOptics NPi-200 infrared pupillometer (NeurOptics Inc, Irvine, California). After infrared measurement of initial pupil diameter, the pupillometer delivers a flash of visible white light. The amplitude of PLR and minimum pupil diameter are measured by the device, and the instrument displays time-stamped numerical data. These include maximum and minimum diameter of right and left pupil as well as Neurological Pupil index (NPi), an algorithmic measure of reactivity graded against a normative model of pupil reactivity. Neurological Pupil index greater than 3 is consistent with normal, or "brisk" reactivity, and a score below 3 is consistent with "sluggish" pupils. Complete absence of PLR results in an NPi of zero.[10] The device has excellent interrater and interdevice reliability.[11]

Pupillary light reflex data were recorded immediately after ROSC or as close to ROSC as possible where clinically appropriate. A time limit of 1 hour was imposed after which patients were excluded. Measurements were taken by a member of the research team or by a member of critical care nursing staff trained to use the NeurOptics pupillometer as part of their routine clinical assessment. Where NPi was discrepant in right versus left pupil, the worst NPi was used in analysis. The investigators retroactively recorded additional details of the patient's clinical course including duration of cardiopulmonary resuscitation (CPR), medications administered, and patient status at 24 hours after ROSC.

These data were analyzed using descriptive statistics including summary measures and description of distributions. Dependence of NPi on epinephrine dose was modeled using simple linear regression without control for additional variables such as patient characteristics, initial rhythm, or arrest duration. Epinephrine dose was considered as a categorical variable and NPi as a continuous variable. Linear regression was modeled for patients captured within one half-life of epinephrine dose (3 minutes), 5 half-lives or full elimination of epinephrine dose (15 minutes), and for all patients in the sample (1 hour).

Results

During the study period, 79 adult in-hospital cardiac arrests that culminated in ROSC occurred at SBCH. Of these 47 (59%) had pupillometry performed within 1 hour after ROSC. Seven of the 47 did not receive epinephrine and were thus excluded from analysis.

Median age of the 40 remaining patients was 67 (median: 71, range: 27-99) and 22 (55%) were male. Nineteen events were captured in medical and surgical ICUs, 7 on telemetry floors, 5 on general medical/surgical floors, 2 in postanesthesia care unit, and 1 in the cardiac catheterization laboratory. Initial rhythm was ventricular tachycardia/fibrillation or torsades de pointes in 13 patients, asystole in 7, and pulseless electrical activity including pulseless bradycardia in 14. Location of arrest and initial rhythm data were not available for the remaining 6 patients.

Of the 40 patients included in this analysis, pupillometry was performed within 5 minutes of ROSC in 19 (45%) patients, and within 15 minutes of ROSC in 30 (71%) patients. The median time to pupillometry was 6 minutes (interquartile range [IQR]: 2-15 minutes). Patient recruitment and exclusion are detailed in Figure 1.

The duration of CPR prior to ROSC ranged from 2 to 39 minutes (median: 6.5 minutes, IQR: 4.75-13.5 minutes). The doses of epinephrine administered ranged from 1 to 7 mg with an average dose of 2.4 mg (standard deviation [SD]: 1.5 mg) and median dose of 2 mg (IQR: 1-3 mg). In addition to epinephrine, 10 patients also received atropine with doses ranging from 0.5 to 2.5 mg, an average dose of 0.85 mg (SD: 0.61 mg), and median dose of 0.5 mg (IQR: 0.5-1 mg).

Of the 40 patients included in our analysis, only 1 (2.5%) patient had nonreactive pupils (NPi of zero) at first measurement 13 minutes after ROSC; this patient received 5 mg epinephrine and 1 mg atropine. Among the remaining 39 (97.5%) patients with reactive pupils NPi ranged from 0.7 to 4.9 (median: 2.75, IQR: 2.0-3.9). Brisk pupillary responses were noted in 22 of 39 (56%; including one who had received 7 mg epinephrine) and sluggish response in 17 (44%) patients. Table 1 summarizes cumulative dose of epinephrine and atropine per patient as well as their pupillary response.

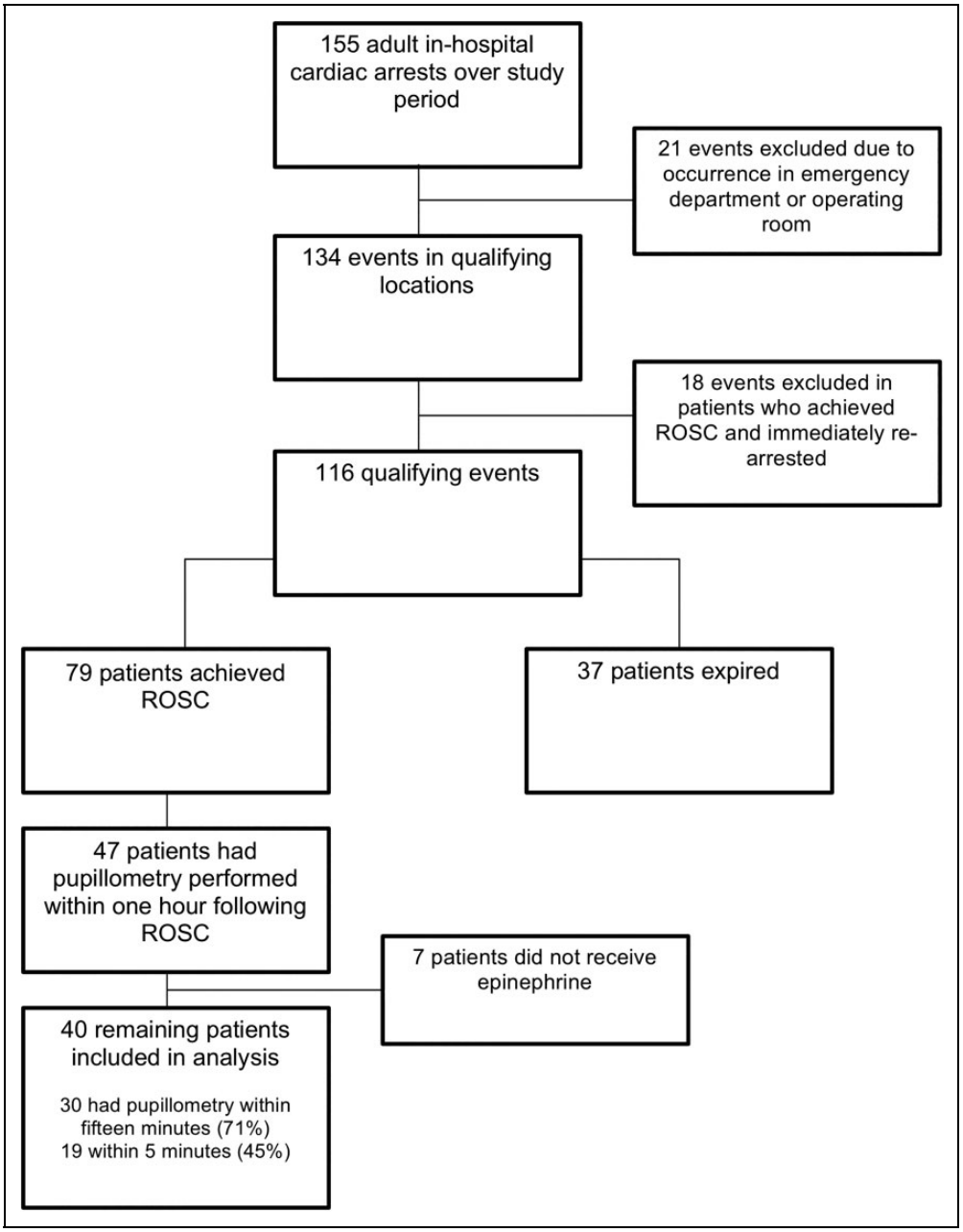

Figure 1. Flow diagram describing the screening, recruitment, and exclusion of patients.

Among patients with reactive pupils, median dose of epinephrine administered was 1 mg (IQR: 1-3) for patients with sluggish pupils and 2 mg (IQR: 1.75-3) for those with brisk pupils defined by NPi. The distribution of NPi versus cumulative dose of epinephrine is displayed in Figure 2 and Figure 3, respectively.

The degree of pupil reactivity was not correlated with cumulative dose of epinephrine administered. Figure 4 demonstrates NPi plotted versus cumulative dose of epinephrine. Linear regression is shown for patients who had pupillometry performed within 3 minutes of last dose of epinephrine (slope of line of best fit 0.1, $R^2 = 0.02$), within 15 minutes of last dose of epinephrine (slope of line of best fit -0.01, $R^2 = 0$), and for the whole study population (slope of line of best fit -0.02, $R^2 = 0$).

Ten patients received atropine in addition to epinephrine, including the sole patient with nonreactive pupils. The remaining 9 (90%) patients, including one who received a total of 2.5 mg atropine, had reactive pupils.

The overall mortality at 24 hours post ROSC was 62%; 25 of 40 patients transitioned to comfort measures or rearrested without ROSC. The sole patient in this cohort with nonreactive pupils rearrested and again achieved ROSC, ultimately transitioned to comfort measures only, and died 77 minutes after pupillometry was performed.

Table 1. Data for All Study Patients Sorted by Time From ROSC to PLR Including Location of Arrest, Initial Rhythm, Cumulative Doses of Epinephrine and Atropine, Duration of CPR Before ROSC, and Worst NPi at First Check.

Location of Arrest	Initial Rhythm	Duration of CPR Before ROSC	Cumulative Dose of Adrenaline (mg)	Cumulative Dose of Atropine (mg)	Time from ROSC to PLR (minutes)	Worst NPi at First Check
Med/Surg	VF	5	2	0.5	00:00	2.3
MICU	Asystole	26	4	-	00:00	3.1
MICU	Asystole	4	1	-	00:00	3.7
SICU	VF/Torsades	7	2	-	00:00	4
Telemetry	VF	16	4	-	00:00	4.2
MICU	Asystole	14	1	-	00:01	2.1
MICU	VF	39	4	0.5	00:01	1.5
MICU	PEA	8	3	-	00:01	2.6
Telemetry	Bradycardia/PEA	5	1	0.5	00:02	1
MICU	Bradycardia/PEA	5	1	2.5	00:02	2.7
Telemetry	PEA	11	5	-	00:02	3.4
MICU	VT/VF	22	2	0.5	00:02	3.8
PACU	PEA	20	3	-	00:02	3.9
Telemetry	PEA	5	1	-	00:02	4.1
SICU	VF/Torsades	3	1	-	00:03	2.8
MICU	VF	10	3	-	00:04	1.92
MICU	PEA	7	2	-	00:04	3.4
MICU	VT/VF	20	2	-	00:05	0.9
Cath lab	Asystole	4	5	-	00:05	2.5
		5	1	-	00:06	0.6
Telemetry	Asystole	11	2	-	00:06	3.9
		19	7	-	00:07	3.4
MICU	VF	6	1	-	00:08	2.48
SICU	VF	2	1	-	00:08	4.7
Telemetry	VF	5	2	-	00:08	4.1
Med/Surg	VT/VF	8	2	-	00:11	1.1
MICU	PEA	7	3	-	00:13	4.7
		3	1	-	00:13	3.1
MICU	VF	25	5	1	00:13	0
Med/Surg	Asystole	13	3	-	00:15	4.2
PACU	PEA	2	2	-	00:16	4
		37	5	1	00:16	0.8
		3	1	-	00:17	1.5
Med/Surg	PEA	4	1	-	00:18	1.7
SICU	PEA	6	5	-	00:20	3.2
MICU	Bradycardia/PEA	6	1	1	00:20	2.3
		4	1	-	00:26	4.4
Med/Surg	Asystole	3	1	-	00:31	2.2
Telemetry	PEA	6	2	-	00:53	1
MICU	Bradycardia/PEA	13	3	0.5	00:56	2.5

Abbreviations: CPR, cardiopulmonary resuscitation; MICU, medical intensive care unit; NPi, Neurological Pupil index; PACU, post-anesthesia care unit; PEA, pulseless electrical activity; PLR, pupillary light reflex; ROSC, return of spontaneous circulation; SICU, surgical intensive care unit; VF, ventricular fibrillation; VT, ventricular tachycardia.

Discussion

Pupil reactivity is an important prognostic indicator in cardiac arrest patients who achieve ROSC.[1,10] Epinephrine and atropine are integral components of ACLS, and thus knowledge of their effect on pupil reactivity is critical for post-arrest prognostication. It is known that both medications cause pupil dilatation, however whether they also block pupillary constriction has not been clearly demonstrated. Our study of adults who achieved ROSC after in-hospital cardiac arrest demonstrates that PLR was not abolished by the use of epinephrine or atropine.

Previous studies have retrospectively addressed the effect of sympathomimetic and parasympatholytic medications on pupil reactivity. In one study of intra-arrest pupil diameter and reactivity, a subset of 8 adult patients received epinephrine, 6 of whom maintained PLR at several checks during CPR and following ROSC and the remaining 2 of whom did not achieve ROSC.[10] An earlier study of children who received atropine during witnessed cardiac arrest commented that the response was present in all patients 30 minutes after ROSC, including those who also received epinephrine.[12] To our knowledge, no dedicated study to date has prospectively examined the

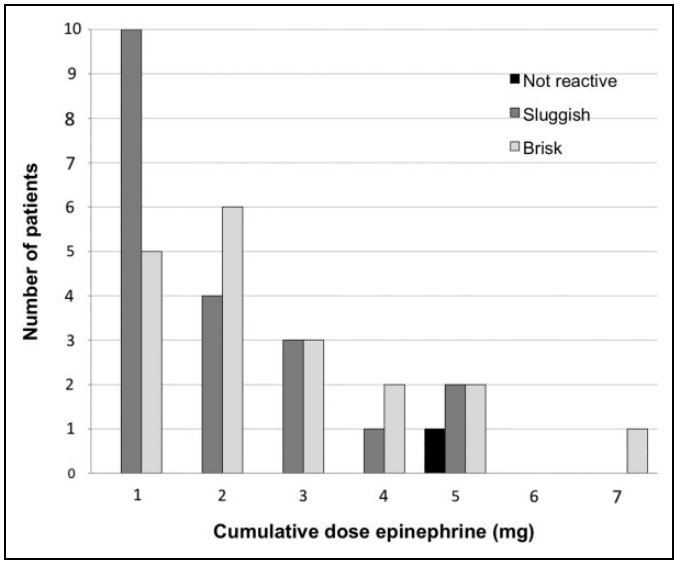

Figure 2. Distribution of patients with brisk, sluggish, or nonreactive pupils based on cumulative dose of epinephrine.

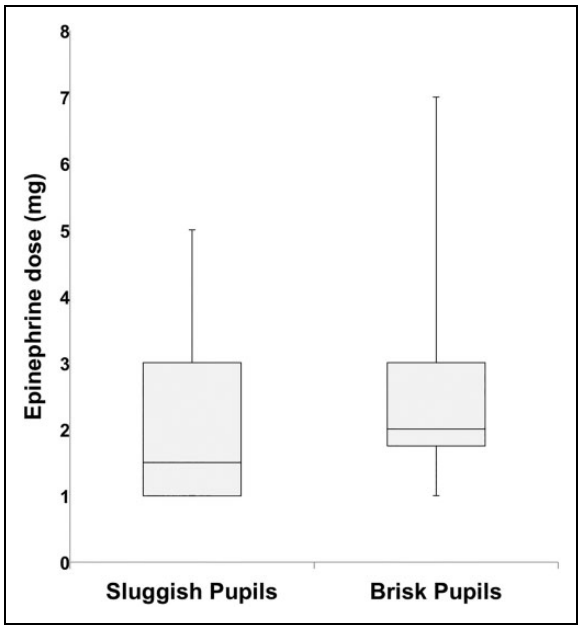

Figure 3. Box plot representation of median dose epinephrine with interquartile ranges for patients with sluggish pupil response (NPi >0 and <3) and brisk pupil response (NPi $\geq$3). Error bars represent upper and lower limits of each group. NPi indicates Neurological Pupil index.

impact of epinephrine and atropine on PLR after cardiac arrest.

A significant strength of this study is the short duration from ROSC to pupillometry. Intravenous epinephrine has a half-life of 2 to 3 minutes. We captured PLR measurements within 12 minutes of the last dose of epinephrine in 25 (64%) of 40 patients; these patients were within 4 half-lives of their last dose of epinephrine and were likely still experiencing its effects when measurements were obtained.[13] All 25 had reactive pupils, including 15 who had PLR checked within 3 minutes, or 1 half-life of the last dose. We believe that this provides strong evidence that exogenous epinephrine does not abolish PLR. In contrast to epinephrine, the half-life of atropine is significantly longer at 20 minutes; 9 of 10 patients who were given atropine had pupillometry performed within one half-life of the drug.[13] All but one had reactive pupils, including one patient who had received 2.5 mg of atropine. The effect of dose on degree of reactivity could not be assessed due to small sample size.

Our use of infrared pupillometry in this study was also a significant strength, as it allowed for objective, quantitative, reproducible measurement of the light reflex. Previous reports attributing pupillary areflexia to administration of vasoactive drugs may have been based on pen light examination, which is subjective and has poor sensitivity for subtle reactivity. Studies of PLR in brain death or during CPR have commented on lack of reliability and interrater variability of manual pupil examination, including one which demonstrated that practitioners were inconsistent with their own measurements of duplicated images of pupils.[3,10,14,15] In these studies, as many as two-thirds of reactive pupils assessed by quantitative infrared pupillometry were scored nonreactive by practitioners.[14]

We captured only one absent PLR, which was surprising considering the size of our sample. Previous studies of PLR as a prognostic indicator in postcardiac arrest patients have noted absent PLR after ROSC in approximately 30% to 40% of patients.[6,16,17] These studies, however, included both in-hospital and out-of-hospital cardiac arrest patients. Our sample was entirely composed of inpatients, the majority of whom were monitored on telemetry or in ICUs and had very short times to initiation of CPR. This likely underlies the presence of PLR in almost every patient we assessed.

In the original 1985 Levy paper, 52 (25%) of 210 did not have reactive pupils at initial examination.[1] These numbers, however, were based on manual assessment of pupil reactivity. Even so, absent PLR was recognized to be an important prognostic sign. More recent studies using quantitative pupillometry have demonstrated that presence of PLR during CPR is an important prognostic indicator of survival to ROSC, and post-ROSC PLR is a predictor of neurologic recovery.[10,18,19] As quantitative pupillometry use becomes more widespread in critical care units, it is more important than ever to understand the prognostic utility of absent PLR and to exclude ACLS medications as confounders as we have done in this study.

In order to capture measurements while patients were experiencing the effects of epinephrine, our study protocol called for measurement of PLR as soon after ROSC as possible. The time-sensitive nature of PLR recording and the critical condition of patients in the peri-arrest period were limiting factors in patient recruitment and data collection, as was the presence or absence of a member of the study team or nursing staff familiar with the protocol. Nevertheless data were captured during 59% of qualifying events that occurred during the

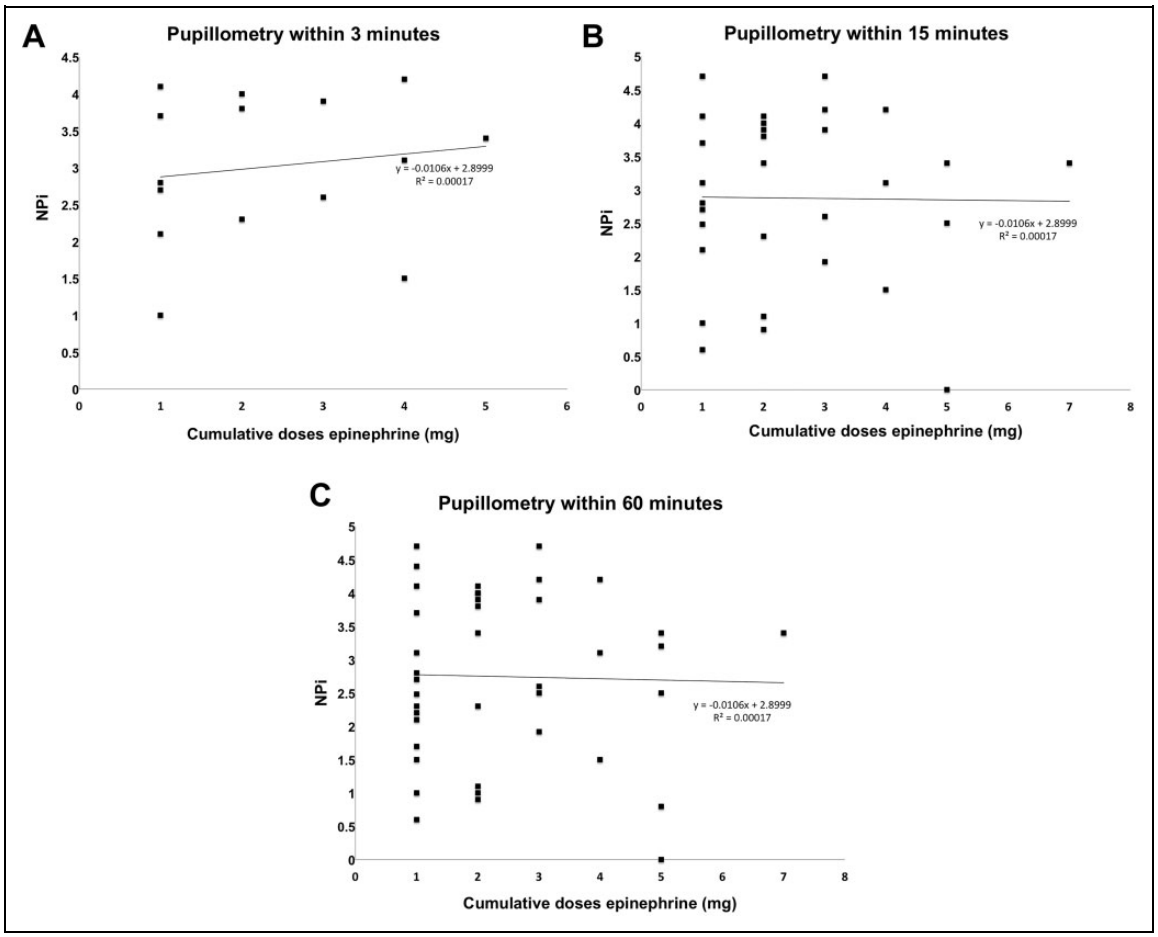

Figure 4. A, Scatter plot of NPi against cumulative doses of epinephrine in milligrams for patients who had PLR checked within 3 minutes of ROSC (n = 19) with line of best fit, slope 0.1037 and $R^2 = 0.0216$. B, Patients with PLR checked within 15 minutes of ROSC (n = 30) with line of best fit, slope −0.0106 and $R^2 = 0.00017$. C, All patients with PLR checked within 1 hour of ROSC (n = 40) with line of best fit, slope −0.0201 and $R^2 = 0.00062$. NPi indicates Neurological Pupil index; PLR, pupillary light reflex; ROSC, return of spontaneous circulation.

study period. Analysis of potential confounding factors, such as blood pH or oxygenation at the time of pupil assessment, was not possible in this study due to variable timing of arterial blood gas measurement. Vasopressor dose, use of opiates or paralytic agents in the peri-arrest period, precipitant of arrest, and underlying rhythm were similarly not analyzed, and intracranial pressure measurements were not available. Rather than a limitation, we consider this a relative strength, as even without controlling for these factors, we saw reactivity in almost all patients who were assessed.

Information regarding post-arrest hospital course and long-term outcome was not collected as part of this study protocol. Our aim, rather, was to determine whether ACLS medications would affect presence or absence of pupil response. This is a critical point that we believe facilitates future study of PLR as a prognostic indicator and to guide post-ROSC care such as targeted temperature management. It is also of significant clinical importance; based on the results we present, physicians making decisions in the post-ROSC period can rely on absent PLR as a poor prognostic indicator even in patients who have received high doses of both epinephrine and atropine.

Conclusion

Epinephrine and atropine given during ACLS do not abolish the PLR in patients who achieve ROSC after in-hospital cardiac arrest. Lack of pupillary response in the post-arrest patient is an important prognostic sign that should not be attributed to these drugs.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: NeurOptics Inc, Irvine, California, loaned a NeurOptics NPi-200 infrared pupillometer to the research team to facilitate the conduct of this study.

ORCID iD

Natalie Achamallah, MD, MA, MS https://orcid.org/0000-0001-8029-2928

References

1. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. *JAMA*. 1985;253(10):1420-1426.
2. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*. 2008;118(23):2452-2483.
3. Olgun G, Newey CR, Ardelt A. Pupillometry in brain death: differences in pupillary diameter between paediatric and adult subjects. *Neurol Res*. 2015;37(11):945-950.
4. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe SNeurology QSSotAAo. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;67(2):203-210.
5. Vlay SC. Acute and semiacute management of cardiac arrest. *Crit Care Clin*. 1989;5(3):643-657.
6. Dhakal LP, Sen A, Stanko CM, et al. Early absent pupillary light reflexes after cardiac arrest in patients treated with therapeutic hypothermia. *Ther Hypothermia Temp Manag*. 2016;6(3):116-121.
7. Larson MD, May J. Effect of asphyxia on the pupils of brain dead subjects. *Resuscitation*. 2002;55(1):31-36.
8. Caglayan HZ, Colpak IA, Kansu T. A diagnostic challenge: dilated pupil. *Curr Opin Ophthalmol*. 2013;24(6):550-557.
9. Gauger GE. What do "fixed, dilated pupils" mean? *N Engl J Med*. 1971;284(19):1105.
10. Behrends M, Niemann CU, Larson MD. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: a case series. *Resuscitation*. 2012;83(10):1223-1228.
11. Zhao W, Stutzman S, DaiWai O, Saju C, Wilson M, Aiyagari V. Inter-device reliability of the NPi-100 pupillometer. *J Clin Neurosci*. 2016;33:79-82.
12. Goetting MG, Contreras E. Systemic atropine administration during cardiac arrest does not cause fixed and dilated pupils. *Ann Emerg Med*. 1991;20(1):55-57.
13. Saeb-Parsy K, Assomull RG, Khan FZ, Kelly E. *Instant Pharmacology*. Chichester, United Kingdom: John Wiley & Sons; 1999.
14. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, Aiyagari V. Interrater reliability of pupillary assessments. *Neurocrit Care*. 2016;24(2):251-257.
15. Kerr RG, Bacon AM, Baker LL, et al. Underestimation of pupil size by critical care and neurosurgical nurses. *Am J Crit Care*. 2016;25(3):213-219.
16. Greer DM, Yang J, Scripko PD, et al. Clinical examination for prognostication in comatose cardiac arrest patients. *Resuscitation*. 2013;84(11):1546-1551.
17. Suys T, Bouzat P, Marques-Vidal P, et al. Automated quantitative pupillometry for the prognostication of coma after cardiac arrest. *Neurocrit Care*. 2014;21(2):300-308.
18. Oddo M, Sandroni C, Citerio G, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. *Intensive Care Med*. 2018;44(12):2102-2111.
19. Solari D, Rossetti AO, Carteron L, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. *Ann Neurol*. 2017;81(6):804-810.