Resuscitation xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Resuscitation

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

Clinical paper

Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series☆,☆☆

Matthias Behrends[a], Claus U. Niemann[a,b], Merlin D. Larson[a,*]

[a] Department of Anesthesia and Perioperative Care, University of California, San Francisco, United States
[b] Department of Surgery, University of California, San Francisco, United States

ARTICLE INFO

Article history:
Received 21 March 2012
Received in revised form 10 May 2012
Accepted 14 May 2012
Available online xxx

Keywords:
Cardiopulmonary resuscitation
Pupillary light reflex
Outcome
Pupillometry

ABSTRACT

Background: The presence or absence of the pupillary light reflex following cardiopulmonary resuscitation has been shown to have prognostic value. We asked whether the light reflex could be objectively measured during cardiopulmonary resuscitation in humans and whether the quality of the reflex was associated with outcome.
Methods: Sixty-seven in-hospital code blue alerts were attended of which 30 met our inclusion criteria. Portable infrared pupillometry was used to measure the light reflex during each code. The reliability of the presence of the light reflex during each code as a predictor of survival and neurological outcome was analyzed statistically using the Barnard's Exact test.
Results: In 25 patients (83%) the pupillary light reflex was detectable throughout or during a part of the resuscitation. Continuous presence of the light reflex or absence for less than 5 min during resuscitation was associated with early survival of the code and a good neurological outcome. In contrast, no patients without a light reflex or with a gradually deteriorating light reflex survived the code and absence of a pupillary light reflex for more than 5 min was associated with an unfavorable outcome.
Conclusion: Portable infrared pupillary measurements can reliably demonstrate the presence and quality of the pupillary light reflex after cardiac arrest and during resuscitation. In our limited case series, the presence of the pupillary light reflexes obtained in serial measurements during resuscitation was associated with early survival and a favorable neurological status in the recovery period.

1. Introduction

One priority for research in cardiopulmonary resuscitation (CPR) is to develop methods for real time physiological monitoring of the circulation and neurologic function, enabling feedback for corrective actions to the resuscitation team.[1] End tidal CO_2,[2] diastolic arterial pressures, palpation of the pulse, analysis of the fibrillation waveform, respiratory movements, gagging, swallowing, and the EEG[3,4] have all been used to gauge the effectiveness of the resuscitation effort but none have been shown to directly measure the adequacy of the central nervous circulation. However, accurate assessment of brain function during resuscitation would be valuable, as corrective action based on measurements of circulation or brain function might decrease the presence of severe neurological deficits in patients who survive.

Pupil size has been studied in this regard but concerns about the effects of drugs on the size of the pupil have curtailed interest in this modality of monitoring the brain stem.[5] Whereas pupil size might be altered by the administration of vasoactive drugs, the pupillary light reflex is likely to be resistant to the effects of intravenously administered drugs[6] but still vulnerable to the depression of cerebral blood flow that accompanies CPR. Previous studies have shown the pupillary light reflex (PLR) to be a robust indicator of neurological outcome in the post-resuscitation period but there are no patient studies on the use of electronically measured light reflexes during CPR.[7–11]

A study in pigs concluded that visual estimates of the PLR during cardiac arrest and resuscitation predicted the likelihood of restoration of cerebral function.[7] Recent improvements in portable infrared pupillometry have enabled light reflexes to be objectively measured in human subjects.[12] The technology can measure light reflexes even when the reflex cannot be seen with the traditional pen light examination.[6,12] We hypothesized that the PLR could be objectively measured during CPR and that the presence of the PLR

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2012.05.013.
☆☆ Abbreviated abstracts of this material were presented at the ASA Annual Meetings in New Orleans, Louisiana (October 17–21, 2009) and San Diego, California (October 16–20, 2010).

* Corresponding author at: Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA 94143-0648, United States.
Tel.: +1 415 885 7412; fax: +1 415 476 9516.
E-mail address: larsonm@anesthesia.ucsf.edu (M.D. Larson).

0300-9572/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.resuscitation.2012.05.013

would serve as a predictor for return of spontaneous circulation (ROSC) and neurological outcome.

2. Methods

The Committee on Human Research at the University of California, San Francisco approved this study that allowed the authors to attend 30 cardiopulmonary resuscitations within the UCSF Medical Center and take pupillary measurements as described below. The data was derived from codes attended between July 2009 through July 2011.

Measurements were performed by the same investigators who had no clinical responsibilities during the time of attendance at the code. All arrests were communicated by the hospital-wide code blue pager system and answered within 2 min. Inclusion criteria included unresponsiveness, absent pulses without chest compressions, and apnea. Resuscitation protocols were determined by the resuscitation team and were not modified by the study.

Pupillary measurements were taken when there was a pause in chest compressions (pulse check, listen for breath sounds, placement of electrodes, EKG check). Investigators did not ask for chest compressions to be stopped at any time in order to take measurements, nor was there a request for prolongation of the pauses in chest compressions. Information obtained from pupillary measurements was not communicated to the resuscitation team.

Pupil measurements ended either when the code terminated or at ROSC. One final measurement was taken following ROSC. If the patient survived the code for three days, additional pupillary measurements were taken. If possible, verbal consent was obtained from the patient at this time and they were given an information sheet that explained the purpose of the study. No patients were excluded from the study because of pre-existing medical conditions.

Pupil diameter and the amplitude of the pupillary light reflex was measured with an infrared pupillometer (Neuroptics, Inc., Irvine, CA).[13] The pupillometer delivers a flash of visible white light of 800 ms duration at the start of each 3.2-s scan. The important features of the PLR are calculated by the instrument from the first 1.5 s of the scan. A time-stamped light reflex is then displayed on a small screen along with numerical data for pupil size and reflex amplitude. Absence of a light reflex was determined by previously described criteria.[6] An algorithm embedded in the software of the instrument has been programmed to consistently record absent light reflexes on artificial pupils that lack a reflex. Brain dead subjects express no light reflexes with infrared pupillometry.[14]

2.1. Statistical analysis

The patients were divided into four groups depending on their conditions post-arrest:

Group 1. Patient survived the code followed by Cerebral Performance Category Scale[15] of 1, 2, or 3 on post arrest day 3. Psychological tests that would evaluate cognitive function and memory were not performed.
Group 2. Patient survived the code with Cerebral Performance Category of 4, or 5 on the third post-arrest day 3. The primary difference between these patients and those in Group 1 is that they had no meaningful interaction with the environment. Examination was performed without pharmacological sedation.
Group 3. Patient survived the code but died within three days post-arrest. No neurological testing was performed.
Group 4. The patient did not survive the code. No return of spontaneous circulation during resuscitation.

Previous studies of in-hospital cardiac arrest have reported that approximately 1/3 survive the code to hospital discharge.[16] By studying 30 codes we calculated that approximately 10 of these patients would survive with favorable outcomes and form a cohort to compare light reflexes to those patients with unfavorable outcomes.

We separated patients into two categories based upon absence of a light reflex less than or more than 5 min. Our rationale for this time was based upon previous reports showing that ischemic times of 5 min leads to depletion of high-energy phosphate levels,[17] increases in intracellular calcium,[18] and profound disturbances in neuronal electrochemical gradients.[19] Accordingly we created two 2×2 contingency tables to test for the following two specific hypotheses:

Hypothesis 1 *(:)*. PLR (present throughout or absent less than 5 min) during resuscitation predicts early survival of CPR (ROSC).

Hypothesis 2 *(:)*. PLR (present throughout or absent less than 5 min) during resuscitation predicts differences in CPC scores 72-h after cardiac arrest.

To determine if there were nonrandom associations between the two categorical variables (outcome and duration of absent reflexes), we performed Barnard's exact probability tests. The Barnard's test uses 2×2 contingency tables and calculates the exact p-value of the null hypothesis.[20] All statistical calculations were performed with Matlab.[21]

3. Results

The authors attended 67 codes to complete the study. Thirty-seven of the codes were not appropriate because they did not meet our inclusion criteria. The excluded cases included respiratory depression (13), fainting (10), seizures (2), and obtundation from drug overdose (12). The remaining thirty cases were included in our analysis and their vital information is summarized in Table 1. Retrospective review of physical examinations performed by the admitting physician prior to the arrests documented the presence of a PLR on all patients. Pre-existing medical conditions that potentially might alter pupillary reflexes in these 30 patients were antihypertensive medications (43%), end stage renal disease (40%), diabetes (30%), previous eye surgery (10%), status post craniotomy (10%), intraocular lenses (7%), and legal blindness from retinal or optic nerve disease (7%).

Duration of the codes from arrival to ROSC or termination of the code varied from 1 min to 60 min with a median of 11 min and interquartile range of 4–17.5 min. The average interval between measurements for all patients was $1.9\,\text{min} \pm 1.3\,\text{min}$; both the mode and median were 1 min.

3.1. Pupillary light reflex measurements

A pupillary light reflex was detectable during CPR in 25 of 30 cases (83%); only five patients were without a pupillary light reflex at any time during CPR. Of those 25 patients with pupillary light reflexes, 9 patients had a PLR at all times during CPR and 4 patients had an intact PLR at the beginning that was subsequently lost. In 8 patients there was no initial PLR but it recovered in less than 5 min, whereas 4 patients with a recovered PLR had missing light reflexes for more than 5 min (range: 12–60 min).

The average pupil size in patients with a PLR was 4.3 ± 1.2 mm, whereas the average PLR was 0.44 ± 0.3 mm in amplitude. Average pupil size in patients with no PLR at any time was 4.7 ± 0.6 mm.

Please cite this article in press as: Behrends M, et al. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series. Resuscitation (2012), http://dx.doi.org/10.1016/j.resuscitation.2012.05.013

Table 1
Summary of demographics, *probable* causes for cardiac arrest, and treatment during resuscitation.

Patient #	Monitored	Age	Sex	Rhythm	Shock	Vasoactive drugs	NMB	Prob. cause for arrest	Cooled	Group 1	Group 2	Group 3	Group 4
Light reflex present													
1[a]	+	61	M	VF	1×	**A, Epi**	+	PE	+	+			
2	–	79	M	PEA	–	Epi	–	PT	–			+	
3	–	20	F	PEA	–	Epi	–	DR	–	+			
4	+	58	M	VF	6×	**Epi**	–	AMI	–			+	
5	+	47	F	PEA	–	Epi	–	MOF	–			+	
6	+	42	F	As	–	–	–	AMI	+			+	
7	+	42	F	PEA	–	**Epi**, NE, V	–	MOF	–			+	
8	–	78	M	PEA	–	–	–	EH	–	+			
9	+	41	M	PEA, As	–	NE, D, NS	–	MOF	–				+
Light reflex present to absent													
10	+	57	M	VF	5×	Epi, A, Am	–	? PE	–				+
11	+	48	F	PEA	–	**Epi**	–	MOF	–				+
12	–	43	F	PEA	–	Epi	–	AMI	–				+
13	+	60	M	VF	4×	NA, V, NS	–	AMI	–				+
Light reflex absent 5 min or less, then present													
14	+	54	M	VF	4×	**Epi**, A	–	AMI	+	+			
15	+	68	M	PEA	–	Epi, A	+	MOF	–			+	
16	+	79	M	VF	6×	**Epi**	–	MMI	–			+	
17	+	36	M	As	–	Epi, NE, V, NS	–	MOF	–			+	
18[a]	+	47	F	PEA	–	**Epi**, V	+	MIH	–	+			
19	+	67	M	PEA	–	Epi, A	+	AMI	–	+			
20	+	47	F	PEA	–	Epi	+	CIA	–	+			
21	+	68	M	VT	2×	Epi, A	–	AMI	–			+	
Light reflex absent more than 5 min, then present													
22	+	78	M	VF	2×	**Epi**	–	AMI	–		+		
23	–	66	M	VF	1×	Epi, A, tPA	–	PE	+			+	
24[a]	+	28	M	As	–	Epi, A	+	DR	+		+		
25	–	27	M	PEA	–	Epi	–	AMI	–		+		
Light reflex absent													
26	+	83	M	As	–	A	–	AMI	–				+
27	–	28	F	VF	4×	A, Epi, V,	–	RAA	–				+
28	+	60	M	PEA	–	Epi, A	–	AMI	–				+
29	+	56	M	PEA	–	NE, Epi, D, NS	–	MOF	–				+
30	–	82	F	As	–	Epi	–	AMI	–				+

Abbreviations: NMB: neuromuscular blockade, As: asystole, PEA: pulseless electrical activity, VF: ventricular fibrillation, VT: ventricular tachycardia, A: atropine (over 10 mg is bold), Epi: adrenaline (over 5 mg is in bold, large type), NE: noradrenaline (norepinephrine), D: dopamine, V: vasopressin, tPA: tissue plasminogen activator, Am: amiodarone, NS: neosynephrine, AMI: acute myocardial infarction, MOF: multiple organ failure, PE: pulmonary embolus, CIA: catheter induced arrhythmia, MIH: massive intraoperative hemorrhage, EH: epidural hematoma, DR: drug reaction, PT: pneumothorax, RAA: ruptured aortic aneurysm.

[a] Patient anaesthetized, no expired CO_2 prior to chest compressions.

3.1.1. Interaction between PLR and drugs administered during CPR

In 6 of 8 cases adrenaline was administered in excess of 5 mg, but the light reflex was not blocked. The two patients given high dose adrenaline with no light reflex both died. In one case (#1) atropine was given in a total dose of 12 mg together with an excess of 5 mg of adrenaline, and the light reflex was not blocked (amplitude of PLR = 0.3 mm), although the pupil was dilated to 6 mm. In this case, as well as with several others in this case series, the resuscitation team considered the light reflex to be absent with the traditional pen light examination. Muscle relaxants did not block the light reflex (Fig. 1 and Table 1).

3.1.2. Resuscitation outcome

Return of spontaneous circulation was achieved in 20 patients (Groups 1–3; 63%); the remaining 10 patients were categorized as Group 4 (37%). Of the 20 early survivors, ten patients were still alive after 72 h. Seven (23%) of these patients had no neurological deficits on the third post arrest day (CPC scores of 1, Group 1), and three patients had new neurological deficits on post arrest day three, that included failure to follow verbal commands (CPC scores of 4, Group 2). Ten initial survivors of the code died within 72 h due to cardiopulmonary complications (Group 3). Group 3 patients were commonly sedated and on ventilatory support thus preventing an accurate assessment of neurological status.

3.2. Association between PLR and outcome

Patients with more favorable neurological outcomes after 72 h (Group 1) typically had increasing amplitude of the light reflex

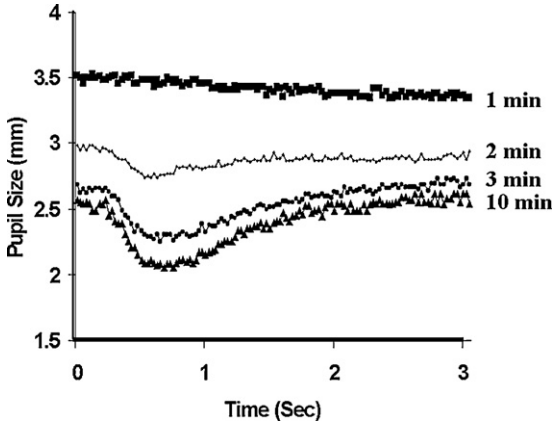

Fig. 1. Cardiac arrhythmia with absent pulses and loss of consciousness (Patient #20). At the start of the code there was no pupillary light reflex. Following chest compressions, neuromuscular paralysis, and subsequent endotracheal intubation, sinus rhythm was re-established and the pupillary light reflex returned into the normal range.

Please cite this article in press as: Behrends M, et al. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series. Resuscitation (2012), http://dx.doi.org/10.1016/j.resuscitation.2012.05.013

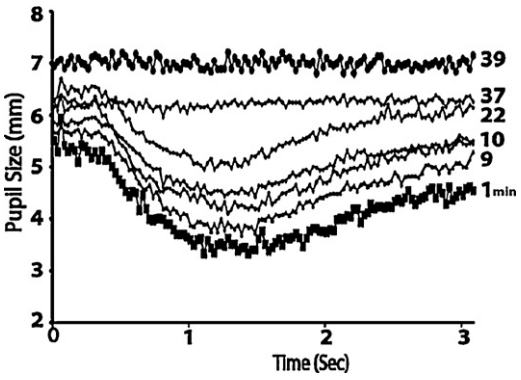

Fig. 2. Repeated measurements in a patient who collapsed when getting out of bed (Patient #10). Selected pupillary measurements are shown, starting 1 min after the code started (times after start of the code are shown on the right side of the graph). The pupillary light reflex deteriorated over the course of the resuscitation. This patient died without return of spontaneous circulation (Group 4).

during CPR. The PLR was either present throughout the code or absent for less than 5 min. Median code durations in these Group 1 patients was 7 min (inner quartile – 9.5 min, range: 4–42 min). Patients who did not survive the code (Group 4) either had absent light reflexes throughout the code ($N = 5$) or a trend of decreasing amplitude in the light reflexes until the reflex was absent (Table 1). Fig. 1 shows the light reflex changes in a Group 1 patient whereas Fig. 2 shows the light reflex changes in a Group 4 patient.

Thirteen patients survived the code (ROSC achieved) but had undesirable outcomes (Groups 2 and 3). The three patients with new neurological deficits on day three (Group 2, #22, 24, 25) had missing light reflexes for more than 5 min. The other patient with a missing light reflex for more than 5 min (#23, see Table 1 and Fig. 3) had missing light reflexes for 40 min and died on the 2nd post arrest day without regaining consciousness. Complete data on light reflexes, drugs administered, and outcome are provided in Table 1.

To test whether the PLR predicted survival and a favorable neurological outcome, two-tailed Barnard's Exact tests were performed on 2×2 contingency tables shown in Table 2. Presence of the pupillary light reflex predicted early survival from resuscitation (Hypothesis 1; $p = 0.0002$). In those patients who survived resuscitation for 3 days, the presence of the pupillary light reflex during resuscitation was an excellent predictor for a favorable neurological outcome (Hypothesis 2; $p = 0.002$, using Barnard's Exact Test).

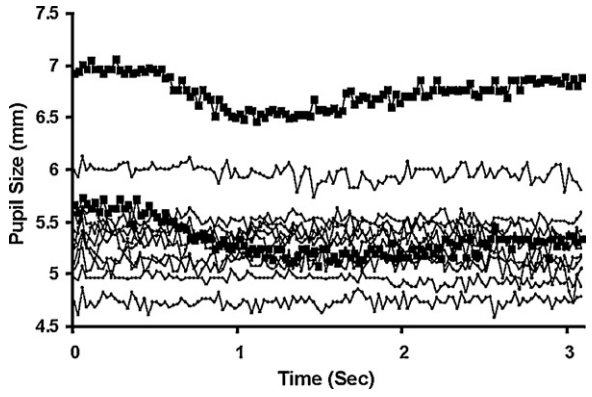

Fig. 3. Ventricular fibrillation (Patient #23). The thin lines represent absent light reflexes measured during 39 min of unsuccessful resuscitation. Following administration of tissue plasminogen activator spontaneous circulation was established. The measurements represented by the black thick lines were taken minutes after ROSC. Patient died on 2nd post arrest day without regaining consciousness.

4. Discussion

Our study demonstrates that the pupillary light reflex can be measured with infrared pupillometry in humans during CPR, and its presence was associated with a favorable neurological outcome. Prolonged absence of the light reflex predicted an unfavorable outcome even if ROSC was achieved. Our findings in patients undergoing cardiopulmonary resuscitation differ dramatically from those observed in brain dead human subjects[6,22] as the primate pupillary light reflex requires a path through the brain, a conclusion reached over 250 years ago by the Scottish physician Robert Whytt.[23]

Previous studies that have examined the relationship between the PLR and recovery from cardiac arrest have used the traditional pen light examination,[24,25] which often will miss reflexes with amplitudes below 0.3 mm.[6] Small sluggish reflexes can be detected with infrared pupillometry that are impossible to appreciate with simple visual inspection of the eye. Our average reflexes were 0.44 mm, amplitude that is readily detected with infrared pupillometry (see Figs. 1 and 3).

We were surprised to find such a high percentage of intact (83%) light reflexes in the low cardiac output state that accompanies CPR. Vision is impaired early as cerebral blood flow drops into the critical range. For example, "blackout" is often used as a lay term for syncope. None of our patients that survived intact were conscious during CPR and none had visual experiences to relate; yet with several cases the light reflexes were remarkably robust (Figs. 1 and 2). The light reflex is one of the most sensitive reflexes in the human body; under the proper lighting conditions a light reflex can be observed at light intensities near the visual threshold.[26] Two patients in this series were legally blind but both had detectable light reflexes at some time during the resuscitation.

It has recently been demonstrated that humans have intrinsically photoreceptive ganglion cells that contribute significantly to the light reflex.[27–29] This is in contrast to the primary visual receptors (rods and cones) that require additional synaptic connections (amacrine, horizontal, bipolar cells) prior to the excitation of ganglion cells that leave the retina *via* the optic nerve. These additional synaptic events in the retina that are necessary for vision may account for the differential effect of reduced cerebral perfusion on vision and the light reflex.

Investigations on use of the PLR to assess brainstem function during CPR cannot be performed with the commonly used mammalian laboratory animals (cat, dog, rat) because their iris musculature is intrinsically light sensitive and this peripheral effect accounts for a small portion of the complete reflex.[30] In addition, the cat iris is exquisitely sensitive to circulating epinephrine.[31] These shortcomings of animal models highlight the need for human data on the PLR as a measure of midbrain function during low cardiac output states.

Some investigators who used traditional pen light examinations of the light reflex have attributed pupillary areflexia during or after cardiac arrest to the administration of vasoactive drugs such as atropine or adrenaline, or to the use of neuromuscular blocking agents. We did not observe a depressant effect of high-dose adrenaline on the PLR, nor did we observe a depressant effect of neuromuscular blocking agents thus lending support to reports that show no effect of neuromuscular blocking agents on the PLR.[32] Although recent American Heart Association (AHA) guidelines for ACLS do not recommend atropine or other anticholinergics for resuscitation from cardiac arrest,[33] these agents have often been implicated in pupillary areflexia when they have been administered for bradycardia. Topical anticholinergic agents such as atropine can block the light reflex but the intravenous dose that totally blocks the light reflex measured with infrared pupillometry is unknown.

Please cite this article in press as: Behrends M, et al. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series. Resuscitation (2012), http://dx.doi.org/10.1016/j.resuscitation.2012.05.013

Table 2
2 × 2 contingency tables. Numbers refer to patients listed in Table 1.

Hypothesis 1: The pupillary light reflex during resuscitation predicts early survival of CPR (ROSC)		
	ROSC – Groups 1–3	No ROSC – Group 4
PLR present or only missing for less than 5 min	1, 2, 3, 4, 5, 6, 7, 8, 14, 15, 16, 17, 18, 19, 20, 21[a]	9
PLR missing, deteriorating or absent for more than 5 min	22, 23, 24, 25	10, 11, 12, 13, 26, 27, 28, 29, 30

Hypothesis 2: The pupillary light reflex during resuscitation predicts neurological outcome in 3-day survivors of CPR. Groups 3 and 4 (20 patients) have been removed from analysis because they did not survive to post arrest day 3. Group 1 patients were all Cerebral Performance Category 1		
	Group 1 – no deficit	Group 2 – deficit
PLR present or only missing for less than 5 min	1, 3, 8, 14, 18, 19, 20[b]	
PLR missing, deteriorating or absent for more than 5 min		22, 24, 25

[a] PLR present or missing for less than five min predicts ROSC, $P = 0.0002$.
[b] PLR present or missing for less than 5 min predicts favorable outcome on post arrest day 3, $P = 0.002$.

In one of our cases, 12 mg of intravenous atropine was unable to block the reflex, although the pupil was dilated. One other report noted that atropine does not block the light reflex during CPR.[34]

The correlation of the presence of a light reflex and the ability to follow verbal commands in the post-resuscitation period might have an explanation based upon the proximity of the pupilloconstrictor nucleus to vital centers of the brainstem. The reflex center for the PLR lies embedded within the periaqueductal gray matter (PAG) of the rostral mesencephalon. The integrity of the PAG is essential for the maintenance of consciousness so an extended loss of blood flow to this area of the brain would be expected to interfere with the ability to maintain a state of awareness and also to damage the reflex center for the PLR.

From our data we are unable to define a time beyond which absence of a light reflex during CPR would portend an unfavorable neurological outcome. We confirm the report by Steen-Hansen et al. who showed that absence of a light reflex on the initial examination does not preclude a full neurological recovery.[5] The limitation of this study is that we were unable to associate the return of pupillary light reflexes during resuscitation with other measures that are sometimes used to gauge the effectiveness of the resuscitation effort. End tidal CO_2 was not measured on all of our cases and often the measures were confounded by inability to secure a closed system and by large differences in minute ventilation. Other measures such as gagging, breathing, swallowing, and eye movements were obscured by the use of muscle relaxants in 20% of our cases. Electronic pupillometry is the first tool that enables a qualitative and quantitative measure of midbrain function in patients undergoing cardiopulmonary resuscitation. Other measures used to assess the quality of the resuscitation effort such as gasping, coughing, eye movements, calorics, and the pulse check cannot be given numerical values.

Absence of the light reflex cannot be used as an indication to stop resuscitation. In most cases pupillary areflexia indicates severe depression of midbrain function and measures should be undertaken to correct the resuscitation plan. Although absence of the light reflex predicted a bad outcome in our study group, there are rare patients who have no light reflex and are awake and have no other neurological deficits.[35] On the other hand, the presence of light reflex indicates that the patient is not brain dead and if the reflex rapidly improves as the resuscitation proceeds, in our small sample of patients, this finding predicts a favorable neurological outcome, if ROSC can be achieved.

In conclusion, we were able to measure the light reflex objectively during CPR with a portable infrared pupillometer. Serial measurements of the light reflex were useful in predicting early survival from resuscitation and the neurological outcome in this series of 30 patients.

Funding

Financial support was obtained from the Department of Anesthesiology and Perioperative Care, University of California, San Francisco.

Conflict of interest statement

The authors have no conflicts of interest.

Acknowledgments

The authors thank Jon M. Aldrich, MD and Michael Gropper, MD, respectively Chair of the Code Blue Committee and Director of the Intensive Care Unit at UCSF Moffitt-Long Hospital for help in designing the study.

References

1. Gazmuri RJ, Nadkarni VM, Nolan JP, et al. Scientific knowledge gaps and clinical research priorities for cardiopulmonary resuscitation and emergency cardiovascular care identified during the 2005 International Consensus Conference on ECC [corrected] and CPR science with treatment recommendations: a consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, and the New Zealand Resuscitation Council); the American Heart Association Emergency Cardiovascular Care Committee; the Stroke Council; and the Cardiovascular Nursing Council. Circulation 2007;116:2501–12.
2. Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. N Engl J Med 1997;337:301–6.
3. Fatovich DM, Jacobs IG, Celenza A, Paech MJ. An observational study of bispectral index monitoring for out of hospital cardiac arrest. Resuscitation 2006;69:207–12.
4. Azim N, Wang CY. The use of bispectral index during a cardiopulmonary arrest: a potential predictor of cerebral perfusion. Anaesthesia 2004;59:610–2.
5. Steen-Hansen JE, Hansen NN, Vaagenes P, Schreiner B. Pupil size and light reactivity during cardiopulmonary resuscitation: a clinical study. Crit Care Med 1988;16:69–70.
6. Larson MD, Muhiudeen I. Pupillometric analysis of the 'absent light reflex'. Arch Neurol 1995;52:369–72.
7. Zhao D, Weil MH, Tang W, et al. Pupil diameter and light reaction during cardiac arrest and resuscitation. Crit Care Med 2001;29:825–8.
8. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic–ischemic coma. JAMA 1985;253:1420–6.
9. van Hoeyweghen RMA, Bossaert L. Decision making to cease or to continue cardiopulmonary resuscitation. Resuscitation 1989;17S:S137–47.
10. Longstreth Jr WT, Diehr P, Inui TS, Jorgensen EO, Malchow-Moller AM. Prediction of awakening after out-of-hospital cardiac arrest cerebral prognostic signs during cardiopulmonary resuscitation. N Engl J Med 1983;308:1378–82.
11. Condemi A, Donatiello G, Mauro M, et al. Importance of pupillary and photomotor reflexes in cardiac resuscitation. Minerva Anestesiol 1981;47:885–90.
12. Du R, Meeker M, Bacchetti P, et al. Evaluation of the portable infrared pupillometer. Neurosurgery 2005;57:198–203, discussion 198–203.
13. Meeker M, Du R, Bacchetti P, et al. Pupil examination: validity and clinical utility of an automated pupillometer. J Neurosci Nurs 2005;37:34–40.

Please cite this article in press as: Behrends M, et al. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series. Resuscitation (2012), http://dx.doi.org/10.1016/j.resuscitation.2012.05.013

14. Larson MDMI. Pupillometric analysis of the "absent light reflex". Arch Neurol 1995;52:369–72.
15. Okada K, Ohde S, Otani N, et al. Prediction protocol for neurological outcome for survivors of out-of-hospital cardiac arrest treated with targeted temperature management. Resuscitation 2012;83:734–9.
16. Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation 2003;58:297–308.
17. Siesjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part I: Pathophysiology. (1992). J Neurosurg 2008;108:616–31.
18. Silver IA, Erecinska M. Intracellular and extracellular changes of $[Ca^{2+}]$ in hypoxia and ischemia in rat brain in vivo. J Gen Physiol 1990;95:837–66.
19. Heuser D, Guggenberger H. Ionic changes in brain ischaemia and alterations produced by drugs. Br J Anaesth 1985;57:23–33.
20. Mehta CR, H JF. Exact power of conditional and unconditional tests: going beyond the 2×2 contingency table. Am Stat 1993;47:91–8.
21. Trujillo-Ortiz A, Hernandez-Walls A, Castro-Perez L, et al. Barnardexactest: Barnard's Exact Probability Test. A MATLAB file. A MATLAB file http://www.mathworks.com/mathlabcentral/fileexchange/loadFile; 2004.
22. Yang LL, Niemann CU, Larson MD. Mechanism of pupillary reflex dilation in awake volunteers and in organ donors. Anesthesiology 2003;99:1281–6.
23. Whytt R. An essay on the vital and other involuntary motions of animals. Edinburgh: T Beckert, Auld and Smellie; 1751.
24. Jorgensen EO, Malchow-Moller AM. Cerebral prognostic signs during cardiopulmonary resuscitation. Resuscitation 1978;6:217–25.
25. Jorgensen EO. Course of neurological recovery and cerebral prognostic signs during cardio-pulmonary resuscitation. Resuscitation 1997;35:9–16.
26. Loewenfeld IE. The pupil: anatomy, physiology and clinical applications. Detroit: Wayne State University Press; 1993.
27. Gamlin PD, McDougal DH, Pokorny J, et al. Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. Vision Res 2007;47:946–54.
28. Kardon R, Anderson SC, Damarjian TG, et al. Chromatic pupil responses: preferential activation of the melanopsin-mediated versus outer photoreceptor-mediated pupil light reflex. Ophthalmology 2009;116:1564–73.
29. Park JC, Moura AL, Raza AS, et al. Toward a clinical protocol for assessing rod, cone, and melanopsin contributions to the human pupil response. Invest Ophthalmol Vis Sci 2011;52:6624–35.
30. Xue T, Do MTH, Riccio A, et al. Melanopsin signalling in mammalian iris and retina. Nature 2011;479:67–73.
31. Bender M, Weinstein E. Actions of adrenaline and acetylcholine on the denervated iris of the cat and monkey. Am J Physiol 1940;130:268–75.
32. Gray AT, Krejci ST, Larson MD. Neuromuscular blocking drugs do not alter the pupillary light reflex of anesthetized humans. Arch Neurol 1997;54:579–84.
33. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S729–67.
34. Goetting MG, Contreras E. Systemic atropine administration during cardiac arrest does not cause fixed and dilated pupils. Ann Emerg Med 1991;20:55–7.
35. Bremner FD, Smith SE. Bilateral tonic pupils: Holmes Adie syndrome or generalised neuropathy? Br J Ophthalmol 2007;91:1620–3.

Please cite this article in press as: Behrends M, et al. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series. Resuscitation (2012), http://dx.doi.org/10.1016/j.resuscitation.2012.05.013