

List of Published Papers Using the NeuroOptics® Pupillometer in Critical Care

1. F.Martínez-Ricarte, A.Castro, M.A.Poca, J.Sahuquillo, L. Expósito, M.Arribas y J.Aparicio, **Infrared pupillometry. Basic principles and their application in the non-invasive monitoring of neurocritical patients**, *Neurología*.2010.doi:10.1016/j.nrl.2010.07.028.

Introduction: Pupil assessment is a fundamental part of the neurological examination. Size and reactivity to light of each pupil should be recorded periodically since changes in these parameters may represent the only detectable sign of neurological deterioration in some patients. However, there is great intraobserver and interobserver variability in pupil examination due to the influence of many factors, such as the difference in ambient lighting, the visual acuity and experience of the examiner, the intensity of the luminous stimulus and the method used to direct this stimulus. In recent years, digital cameras have incorporated infrared devices allowing the development of user-friendly portable devices that permit repeated, non-invasive examination of the pupil size and its reactivity to light with an objective, accessible and inexpensive method. *Development:* The purpose of this review is to describe the fundamentals of infrared pupillometry and discuss potential applications in the monitoring of neurocritical patients. We also present some recommendations in the routine assessment of pupils in neurocritical patients. *Conclusions:* The possibility of evaluating the changes in pupil reactivity in an early, objective and almost continuous way provides a new noninvasive monitoring method. This method could improve the predictive factor of neurological deterioration and the bedside monitoring of the neurological state of the patient, avoiding unnecessary examinations and enabling early therapeutic intervention.

2. Cecil Sandy , Chen Patrick M, Callaway Sarah E, Rowland Susan M, Adler David E and Chen Jeffersen W, **Traumatic Brain Injury: Advanced Multimodal Neuromonitoring From Theory to Clinical Practice**, *Critical Care Nurse*, June 30, 2010; doi: 10.4037/ccn2010226.

No abstract available.

3. Niemann Claus U, Larson Merlin D, **Quantitation of the Pupillary Light Reflex during Cardiopulmonary Resuscitation**, American Society of Anesthesiologists annual meeting abstract A1138, October 20, 2009.

Previous studies during CPR have focused on the size of the pupil which may be confounded by concomitant drug therapy. We focused on the light reflex based upon a recent study (1) showing that following arrest of the circulation, the pupillary light reflex is lost prior to dilation and that return of the light reflex during chest compressions predicts neurologic recovery. Our preliminary data are the first to demonstrate that the pupillary light reflex can be quantified during CPR in humans. Although this study is preliminary with only 12 patients, the trend we observed suggests that the pupillary light reflex can be used as another measure of adequate perfusion of the midbrain during CPR. However, it cannot be stated that absence of the light reflex reflects a hopeless outcome. It appears that sequential measurements during CPR may be more predictive.

4. Li D, Miaskowski C, Burkhardt D, Puntillo K, **Evaluations of physiologic reactivity and reflexive behaviors during noxious procedures in sedated critically ill patients.**, *J Crit Care.*, 2009 Jan 16.

PURPOSE: Sedated patients' responses to noxious stimulation are not well characterized. A standardized measure of nociception for use in the intensive care unit (ICU) is elusive. The study aimed to describe cardiovascular and pupil reactivity and behavioral responses between noxious and nonnoxious procedures in sedated ICU patients. **MATERIALS AND METHODS:** This prospective, descriptive study performed repeated measures using within-subject and crossover techniques. Forty-eight sedated, ventilated cardiac surgery patients from 2 institutions were included. Pupil sizes, heart rate, blood pressure, cortical arousal changes per the bispectral index, and behaviors were recorded at baseline, during, and after a noxious procedure (endotracheal suctioning or turning), and gentle touch. **RESULTS:** The majority of patients was deeply sedated with propofol infusion and were unresponsive or responsive only to physical stimulation. Significant changes in heart rate, pupil size, and bispectral index occurred with the noxious procedure but not with the nonnoxious procedure ($P < .01$). Reflexive behaviors were not evident during both procedures. **CONCLUSIONS:** Certain physiologic reactions and pupil size changes may be potentially useful nociceptive indicators in ICU settings. Further research is needed to determine the clinical parameters of physiologic response change and to evaluate the effects of opioids and sedatives on these physiologic responses.

5. Fountas KN, Kapsalaki EZ, Machinis TG, Boev AN, Robinson JS, Troup EC, **Clinical implications of quantitative infrared pupillometry in neurosurgical patients**, *Neurocrit Care.* 2006;5(1):55-60.

January 4, 2011

List of Published Papers Using the NeuroOptics® Pupillometer in Critical Care

Pupillometry has been widely employed in the evaluation of a large number of pathological conditions, including intracranial pathology. The recent introduction of a portable, user-friendly, infrared pupillometer (ForSite, NeuroOptics Inc., Irvine, CA) has enabled the accurate and reproducible measurement of several pupillary parameters, such as maximum and minimum apertures, constriction and dilation velocities, and latency period. It should be noted that various clinical conditions, especially neurological and ocular diseases, as well as numerous medications, may interfere with the measurements. Furthermore, a number of physiological parameters, such as the intensity of retinal illumination, the level of patient's alertness, the intensity of ambient light, as well as the time of day that the examination is performed may alter the obtained values. The potential implications of pupillometry in the clinical assessment of neurosurgical patients, including its complex relationship to intracranial pressure changes, mandate the undertaking of prospective clinical studies validating the clinical significance of this noninvasive, diagnostic modality.

6. Hults KN, Knowlton SL, Oliver JW, Wolfson T, Gamst A., **A study of pupillary assessment in outpatient neurosurgical clinics.**, J Neurosci Nurs. 2006 Dec;38(6):447-52.

This study compared the accuracy of three methods of assessing pupil diameter. Measurements from the ForSite pupillometer and visual assessments were compared with measurements obtained using a pupil gauge (the standard method). Two sets of measurements were obtained from 65 out-patients at four neurosurgical clinics. The correlation between the three methods showed significance; however, the pupil gauge measurements showed a more significant correlation with measurements from the pupillometer than with visual assessments. Pupil diameter measurements from the pupillometer were larger than those from either the pupil gauge or clinical observation. We conclude that the ForSite pupillometer is an easy-to-use and accurate measure of pupil diameter in a clinic setting. It may be more accurate than the pupil gauge.

7. Boev AN, Fountas KN, Karampelas J, Boev C, Machinis TG, Feltes C, Okosun I, Dimopoulos V, Troup C., **Quantitative pupillometry: normative data in healthy pediatric volunteers.**, J Neurosurg. 2005 Dec;103(6 Suppl):496-500.

OBJECT: The authors describe the prospective use of a new hand-held point-and-shoot pupillometer (NeuroOptics) to assess pupil function quantitatively. **METHODS:** Repetitive measurements were made in 90 pediatric participants ranging in age from 1 to 18 years, providing a total of 100 measurements under ambient light conditions. The participants consisted of 45 patients without known intracranial or ophthalmological pathological conditions as well as 45 volunteers in the outpatient setting. Quantitative pupil measurements were reliably replicated in the study participants. The mean resting pupil aperture was 4.11 mm and the minimal diameter after stimulation was 2.65 mm, resulting in a 36% change in pupil size. The mean constriction velocity was 2.34 mm/second, with a mean dilation velocity of 2.2 mm/second. **CONCLUSION:** Pupil symmetry was impressive in the entire cohort.

8. Du R, Meeker M, Bacchetti P, Larson MD, Holland MC, Manley GT., **Evaluation of the portable infrared pupillometer.**, Neurosurgery. 2005 Jul;57(1):198-203; discussion 198-203.

[No abstract available.]

9. Meeker M, Du R, Bacchetti P, Privitera CM, Larson MD, Holland MC, Manley G., **Pupil examination: validity and clinical utility of an automated pupillometer.**, J Neurosci Nurs. 2005 Feb;37(1):34-40.

Pupillary size and reactivity have long been a critical component of the clinical assessment of patients with neurological disorders. The pupillary examination may provide critical information related to new or worsening intracranial pathology and facilitate prompt intervention to minimize further neuronal damage. With this in mind, intensive care nurses caring for neurologically impaired patients frequently must perform pupillary examinations in concert with assigning a Glasgow Coma Scale score. The purpose of this study was to test the accuracy and reliability of an automated pupillometer compared with the standard manual examination as a preliminary step in assessing the usefulness of automated pupillometry in the critical care setting. Twenty patients in the intensive care units of a teaching hospital were examined by two groups of three examiners using both the manual examination with a penlight or similar light source and a portable automated pupillometer capable of measuring pupil size and reaction. Measurements by a static pupillometer before and after each pupillary examination were used to determine the mean "true" size of the pupil. This study found that the automated pupillometer is more accurate and reliable than the manual examination in measuring pupil size and reactivity. For these reasons, such a device may be a beneficial addition in the clinical assessment of neurologically impaired patients.

10. Larson MD, Berry PD, May J, Bjorksten A, Sessler DL., **Latency of pupillary reflex dilation during general anesthesia.**, 2004 Aug;97(2):725-30.

Areas of insensibility produced by neuraxial anesthesia or peripheral nerve blocks can be detected during general anesthesia by failure of noxious stimulation to trigger pupillary reflex dilation. We examined the latency of pupillary reflex dilation and the effect of fentanyl on the latency of reflex

List of Published Papers Using the NeuroOptics® Pupillometer in Critical Care

dilation during anesthesia in nine volunteers. We hypothesized that the reflex was generated by slowly conducting C nociceptive fibers and would be significantly delayed if a distal dermatome (L(4)) was stimulated compared with a proximal dermatome (C(5)). We also hypothesized that fentanyl would prolong the latency and alter the shape of the reflex. After induction of general anesthesia, pupillary reflex dilation was measured with an infrared pupillometer every 5 min after stimulations of the L(4) and C(5) dermatomes. Fentanyl (3 microg/kg) was then given intravenously. Pupillary reflex dilation latencies were calculated by examining each individual measurement. After 3 h, naloxone (400 microg) was given intravenously; anesthesia was then discontinued. Pupillary reflex dilation had a long latency and consisted of distinct early and late phases. No differences were found between latencies of reflex dilation after simulation of L(4) and C(5) dermatomes either before or after fentanyl administration. Fentanyl at high concentrations essentially eliminated pupillary reflex dilation; but over the 180-min observation period, first early and then late dilation returned. Fentanyl produced a small increase in the latency of the initial early dilation. We conclude that pupillary reflex dilation during anesthesia is not initiated by slowly conducting C fibers and that fentanyl depresses the reflex in a stereotypical manner.

11. Yang LL, Niemann CU, Larson MD., Mechanism of pupillary reflex dilation in awake volunteers and in organ donors., Anesthesiology. 2003 Dec;99(6):1281-6.

BACKGROUND: The mechanism of reflex pupillary dilation was investigated in eight patients who were declared brain dead after rupture of intracranial vascular malformations and in eight awake volunteers. The authors hypothesized that the reflex was primarily a spinal sympathetic reflex that would be blocked by topical application of the alpha1-adrenergic blocking agent dapiprazole and that it would be present in organ donors with intact spinal reflexes and no history of hypoxia. **METHODS:** In volunteers, pupil size was measured with an infrared pupillometer while brief painful electric stimuli were delivered to the finger. Pain was assessed with a visual analog scale and adjusted with each volunteer to equal 3 on a visual analog scale of 0-10. Subjects were studied before and after topical application of the alpha1-adrenergic antagonist dapiprazole. In organ donors, the authors measured pupil size after high-intensity tetanic electric stimulation and in dapiprazole-blocked and -unblocked pupils after surgically induced nociception. **RESULTS:** In volunteers, the pupil dilated 0.43 +/- 0.23 mm after nociceptive stimuli. Dapiprazole eyedrops blocked this dilation, confirming that the reflex in awake humans is primarily a sympathetic reflex. Baseline diameters were 5.7 +/- 0.5 mm before dapiprazole and 4.1 +/- 0.9 mm after dapiprazole. In organ donors, a tetanic electric current failed to dilate the pupil, whereas the skin incision dilated the pupil 0.4 +/- 0.4 mm, but this dilation was not blocked by dapiprazole. **CONCLUSION:** The authors conclude that pupillary reflex dilation, as it is clinically performed in awake subjects by stimulating somatic nociceptors, is a sympathetic reflex. Because it is not present in organ donors, the neural pathway must require a supraspinal component for completion.

12. Taylor WR, Chen JW, Meltzer H, Gennarelli TA, Kelbch C, Knowlton S, Richardson J, Lutch MJ, Farin A, Hulst KN, Marshall LF., **Quantitative pupillometry, a new technology: normative data and preliminary observations in patients with acute head injury.** Technical note., J Neurosurg. 2003 Jan;98(1):205-13.

The authors prospectively used a new hand-held point-and-shoot pupillometer to assess pupillary function quantitatively. Repetitive measurements were initially made in more than 300 healthy volunteers ranging in age from 1 to 87 years, providing a total of 2,432 paired (alternative right eye, left eye) measurements under varying light conditions. The authors studied 17 patients undergoing a variety of nonintracranial, nonophthalmological, endoscopic, or surgical procedures and 20 seniors in a cardiology clinic to learn more about the effects of a variety of drugs. Additionally, the authors carried out detailed studies in 26 adults with acute severe head injury in whom intracranial pressure (ICP) was continuously monitored. Finally, five patients suffering from subarachnoid hemorrhage were also studied. Quantitative pupillary measurements could be reliably replicated in the study participants. In healthy volunteers the resting pupillary aperture averaged 4.1 mm and the minimal aperture after stimulation was 2.7 mm, resulting in a 34% change in pupil size. Constriction velocity averaged 1.48 +/- 0.33 mm/second. Pupillary symmetry was striking in both healthy volunteers and patients without intracranial or uncorrected visual acuity disorders. In the 2,432 paired measurements in healthy volunteers, constriction velocity was noted to fall below 0.85 mm/second on only 33 occasions and below 0.6 mm/second on eight occasions (< one in 310 observations). In outpatients, the reduction in constriction velocity was observed when either oral or intravenous narcotic agents and diazepam analogs were administered. These effects were transient and always symmetrical. Among the 26 patients with head injuries, eight were found to have elevations of ICP above 20 mm Hg and pupillary dynamics in each of these patients remained normal. In 13 patients with a midline shift greater than 3 mm, elevations of ICP above 20 mm Hg, when present for 15 minutes, were frequently associated with a reduction in constriction velocity on the side of the mass effect to below 0.6 mm/second (51% of 156 paired observations). In five patients with diffuse brain swelling but no midline shift, a reduction in constriction velocities did not generally occur until the ICP exceeded 30 mm Hg. Changes in the percentage of reduction from the resting state following stimulation were always greater than 10%, even in patients receiving large doses of morphine and propofol in whom the ICP was lower than 20 mm Hg. Asymmetry of pupillary size greater than 0.5 mm was observed infrequently (< 1%) in healthy volunteers and was rarely seen in head-injured patients unless the ICP exceeded 20 mm Hg. Pupillometry is a reliable technology capable of providing repetitive data on quantitative pupillary function in states of health and disease.