정량적 동공반응계측

김 태 정
서울의대 중환자진료부 신경과

Quantitative pupillometry

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Disclosure

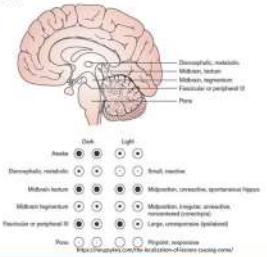
None.

Contents

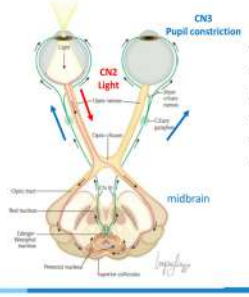
- Introduction
- Quantitative Pupillometry
- Clinical implication of quantitative Pupillometry
- Conclusions

Introduction

- Pupil light reflex: Monitoring neurological status
- Pupil examination: Symmetry & Size
- Anisocoria (unequal pupils)
  - Physiologic anisocoria: 양 쪽 차이 <0.7 mm (20-30%)
  - Non-neuro reasons: scopolamine patch, nebulizer
  - IICP, uncal herniation: Emergency !!
- Large pupil (> 5mm)
  - Antihistamine
  - Anticholinergics
  - Trauma
  - IICP
- Small pupil (< 1mm)
  - Opioid
  - Pontine lesion

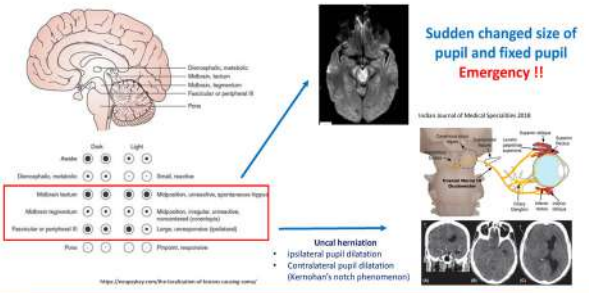


Pupil Light reflex (CN 2 & CN 3)



- Pupil light reflex
- Direct response: prompt, sluggish, fixed
- CN3 손상: light reflex (-)
- 최소 30초 간격을 두고 검진
- NM blocker 투약 중에도 검진 가능
- 이전에 눈 수술 병력이 있으면 이상 소견이 나올 수 있어 initial examination 이 필요

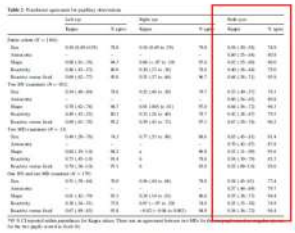
Pupil Light reflex (CN 2 & CN 3)

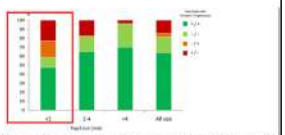


Sudden changed size of pupil and fixed pupil
Emergency !!

Uncal herniation
- Ipsilateral pupil dilatation
- Contralateral pupil dilatation (Kernohan's notch phenomenon)

Limitation of standard pupil examination





Traditional pupil examination: There is limited interrater reliability (60-70%) for scoring pupil reactivity, especially in small size pupil.

Automated quantitative pupillometry

NeurOpticsNPi™®-100/200 (USA)

Neurlight-Algiscan® (France)
Evaluating depth of analgesia

Quantitative pupillometry (NeurOptics®NPi™)

- **Quantitative pupillometry**
- Evaluate pupil size and reactivity
- A hand-held infrared system which automatically tracks and analyzes pupil dynamics (LED light source) - burst of visible light at 1000 lx for 0.8 s
- Storing repeated video images at > 30 frames per second for 3.2 s
- Minimize possible inter-observer variability in the pupillary evaluation

Measuring pupil using pupillometry

1

Right angle to patient's axis vision

2

Press and hold either the RIGHT or LEFT button until the eye is centered on the touchscreen and the display shows a green circle around the pupil.

3

Once the green circle appears, release the button, holding the NPi in place for approximately three seconds

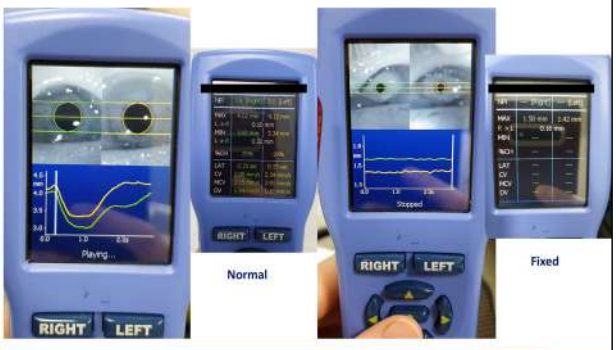
Measuring pupil using pupillometry

Successful measurement

Bad – Recheck !!

Parameters of Automated quantitative pupillometry

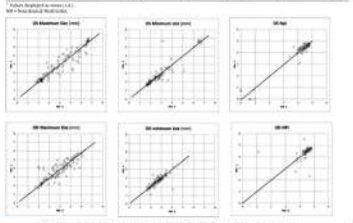
Parameters	Definition	Normal range
MAX	Maximum pupil size before constriction (pupil size)	Asymmetry: 0.5-0.7mm
MIN	Pupil diameter at peak constriction	
%CH = % Change	% of change (Size-MIN) / Size as a %	≥15% - prompt 1-14% - sluggish 0% - fixed
LAT (Latency of constriction)	Time of onset of constriction following initiation of the light stimulus	0.24 - 0.28 sec
CV (Constriction Velocity)	Average of how fast the pupil diameter is constricting measured in millimeters per second	≥0.8-1.5 mm/s
MCV (Maximum Constriction Velocity)	Maximum velocity of pupil constriction of the pupil diameter responding to the flash of light measured in millimeters per second	
DV (Dilation Velocity)	Distance (mm) of redilation divided by duration (seconds) of redilation	~2.83 mm/s
Neurological pupillary index (NPi)	Proprietary algorithm using all parameters to determine pupillary response	Npi 3.0-4.9: normal, prompt Npi <3.0: abnormal NPi: 0: non reactivity



Clinical Study

Inter-device reliability of the NPi-100 pupillometer

Weidan Zhao, Sonja Stutzman, DaiWai Olson, Ciji Saju, Margaret Wilson, Venkatesh Aiyagari



Automated pupillary assessments have a high inter-device reliability by exminations.

Clinical implications of quantitative pupillometry

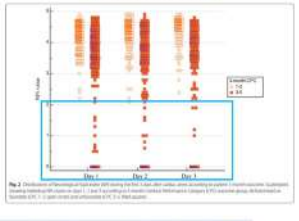
- **Applications in the neurointensive care unit**
  - Post cardiac arrest
  - TBI
  - ICP monitoring (noninvasive method)
  - Stroke
  - Etc..

Cardiac arrest

Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study

- Multicenter study (10 centers)
- Comatose CA patients
- Quantitative Npi and PLR check from 1-3 days after CA
- Outcome: 3-month Cerebral Performance Category (CPC) – good CPC 1-2 vs poor CPC 3-5

NPi ≤ 2 : 51% (95% CI 49–53) negative predictive value and a 100% positive predictive value [PPV; 0% (0–2) false-positive rate], with a 100% (98–100) specificity and 32% (27–38) sensitivity for the prediction of unfavorable outcome.



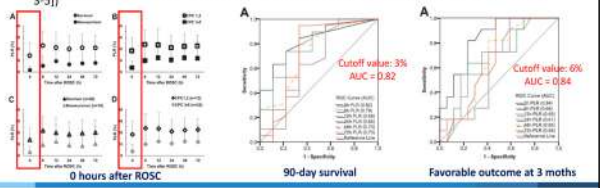
Quantitative NPi had excellent ability to predict an unfavorable outcome from day 1 after CA, with no false positives, and significantly higher specificity than standard manual pupillary examination.

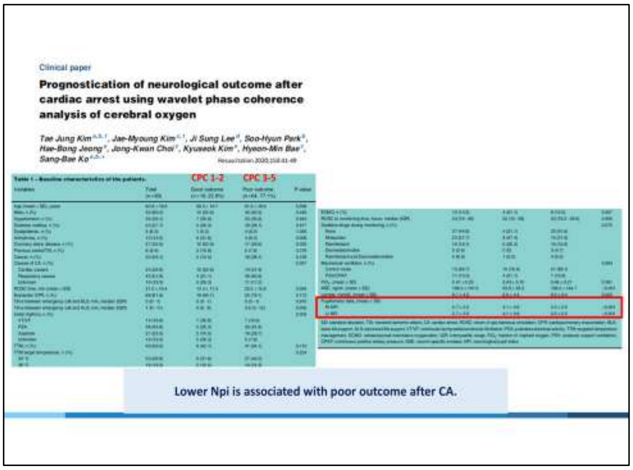
Clinical paper

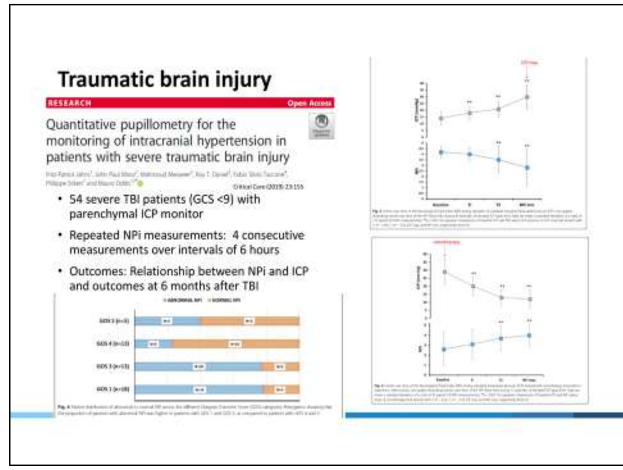
Quantitative assessment of pupillary light reflex for early prediction of outcomes after out-of-hospital cardiac arrest: A multicentre prospective observational study

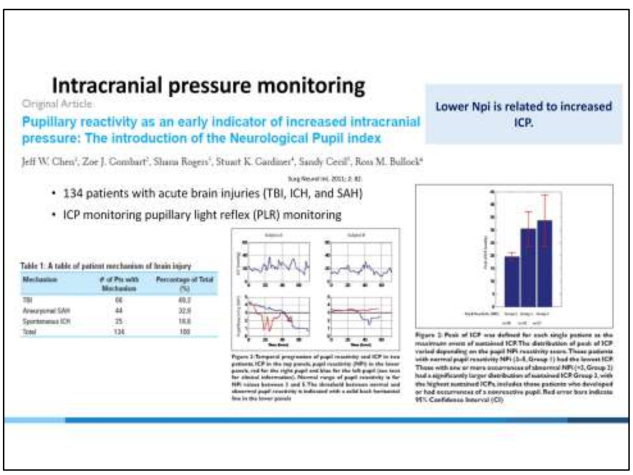
Tomoyoshi Tamura, Jun Namiki, Yoko Sugawara, Katsuhiko Sekine, Kikuo Ye, Takahiro Kanaya, Shoji Yokobori, Rachel Roberts, Takayuki Abe, Hiroyuki Yokota, Junichi Sasaki

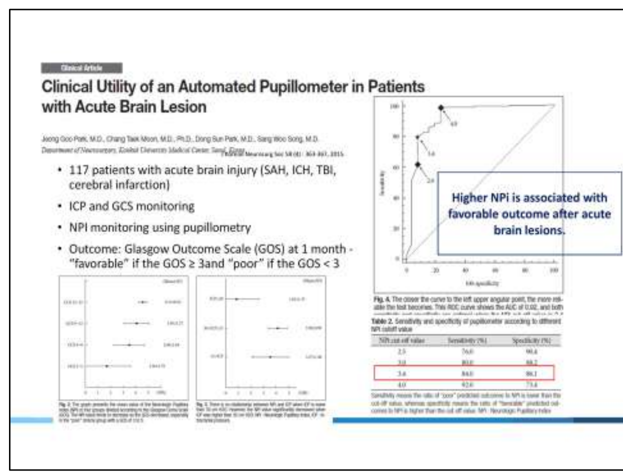
- Fifty patients resuscitated after non-traumatic out-of-hospital CA (OHCA)
- PLR was sequentially measured at 0, 6, 12, 24, 48, and 72 h after ROSC by an automated portable infrared pupillometry.
- Outcomes: 90-day survival and neurological outcome 90 days after CA (good [CPC 1-2], poor [CPC 3-5])

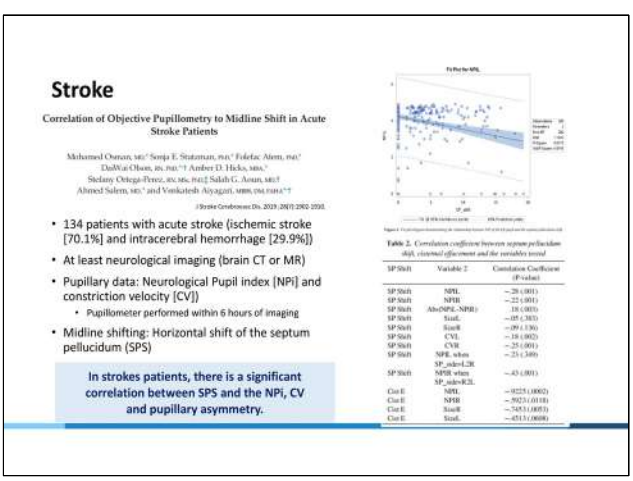


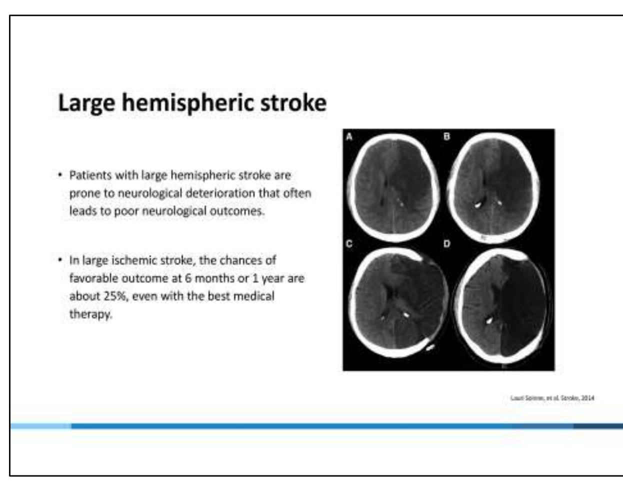

Clinical paper
Prognostication of neurological outcome after cardiac arrest using wavelet phase coherence analysis of cerebral oxygen
Tae Jung Kim, Jae-Myoung Kim, Ji Sung Lee, Soo-Hyun Park, Hae-Bong Jeong, Jong-Kwan Choi, Kyuseok Kim, Hyeon-Min Bae, Sang-Bae Ko
Table 1 – Baseline characteristics of the patients.
CPC 1-2
CPC 3-5
Lower Npi is associated with poor outcome after CA.


Traumatic brain injury
RESEARCH
Open Access
Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury
Critical Care (2019) 23:155
54 severe TBI patients (GCS <9) with parenchymal ICP monitor
Repeated NPi measurements: 4 consecutive measurements over intervals of 6 hours
Outcomes: Relationship between NPi and ICP and outcomes at 6 months after TBI

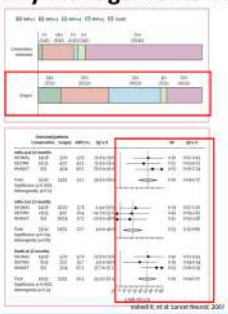

Intracranial pressure monitoring
Original Article
Pupillary reactivity as an early indicator of increased intracranial pressure: The introduction of the Neurological Pupil index
Jeff W. Chen, Zoe J. Gombart, Shana Rogers, Stuart K. Gardiner, Sandy Cecil, Ross M. Bullock
Lower Npi is related to increased ICP.
134 patients with acute brain injuries (TBI, ICH, and SAH)
ICP monitoring pupillary light reflex (PLR) monitoring
Table 1: A table of patient mechanism of brain injury
Mechanism
# of Pts with Mechanism
Percentage of Total (%)
TBI
Aneurysmal SAH
Spontaneous ICH
Total
134
100

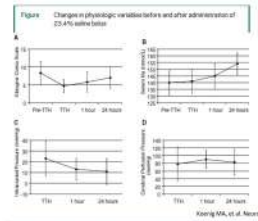

Clinical Article
Clinical Utility of an Automated Pupillometer in Patients with Acute Brain Lesion
117 patients with acute brain injury (SAH, ICH, TBI, cerebral infarction)
ICP and GCS monitoring
NPI monitoring using pupillometry
Outcome: Glasgow Outcome Scale (GOS) at 1 month - "favorable" if the GOS ≥ 3and "poor" if the GOS < 3
Higher NPi is associated with favorable outcome after acute brain lesions.


Stroke
Correlation of Objective Pupillometry to Midline Shift in Acute Stroke Patients
134 patients with acute stroke (ischemic stroke [70.1%] and intracerebral hemorrhage [29.9%])
At least neurological imaging (brain CT or MR)
Pupillary data: Neurological Pupil index [NPi] and constriction velocity [CV])
Pupillometer performed within 6 hours of imaging
Midline shifting: Horizontal shift of the septum pellucidum (SPS)
In strokes patients, there is a significant correlation between SPS and the NPi, CV and pupillary asymmetry.


Large hemispheric stroke
Patients with large hemispheric stroke are prone to neurological deterioration that often leads to poor neurological outcomes.
In large ischemic stroke, the chances of favorable outcome at 6 months or 1 year are about 25%, even with the best medical therapy.
A
B
C
D

Early managements with surgery or osmotherapy





Early management of brain swelling with decompressive surgery or osmotherapy is the main goal of the treatment protocol.

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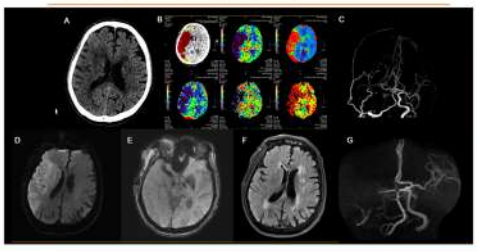
■ Letter to the Editor ■

Implication of Neurological Pupil Index for Monitoring of Brain Edema

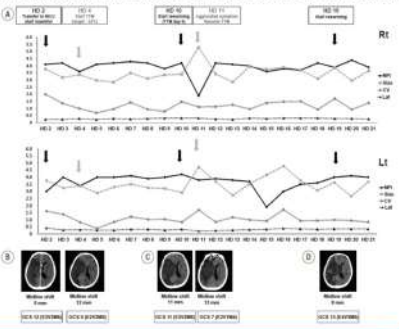
Tae Jung Kim[1,2] and Sang-Bae Ko[1,2]

[1]Department of Neurology, [2]Department of Critical Care Medicine, Seoul National University Hospital, Seoul, Korea



78-year-old man
Rt MCA territory infarction

Serial pupillometer parameters and brain CT of the patient



ORIGINAL WORK

Neurological Pupil Index as an Indicator of Neurological Worsening in Large Hemispheric Strokes

Tae Jung Kim[1,2], Soo-Hyun Park[3], Hae-Bong Jeong[3], Eun Jin Ha[1,2], Won Sang Cho[4], Hyun-Seung Kang[5], Jung Eun Kim[6] and Sang-Bae Ko[1,2]

Neurocrit Care (2020) 33:575–581

- 30 patients with large hemispheric stroke (IS 66.7%, ICH 33.3%)
- Consecutive pupillary response monitoring every 2 or 4 hours in NICU – NPi value
- Outcome: neurological worsening (NIHSS ≥ 4 aggravation)

Figure. Distributions of neurological pupil index (NPi) during monitoring periods after stroke onset according to neurological worsening

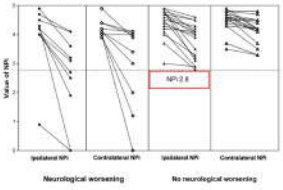


Table 2 The values of neurological pupil index according to neurological worsening

	Neurological worsening (n = 10, 33.3%)	No neurological worsening (n = 20, 66.7%)	P value
Total value of NPi during monitoring (mean ± SD)	3.82 ± 0.57	4.38 ± 0.55	< 0.001
Lowest value of NPi during monitoring on the ipsilateral side, median (IQR)	2.9 (1.4–3.7)	4.1 (3.2–4.2)	0.009
Lowest value of NPi during monitoring on the contralateral side, median (IQR)	3.5 (1.8–4.2)	4.2 (3.5–4.5)	0.031
Percent change of NPi from previous value in the ipsilateral side, median (IQR)	29.5 (20.0–66.1)	11.1 (5.7–25.0)	0.006
Percent change of NPi from previous value in the contralateral side, median (IQR)	18.7 (5.7–54.0)	8.7 (2.3–12.5)	0.050

IQR interquartile ranges, NPi neurological pupil index, SD standard deviation

Table 3 Changes of neurological pupil index values and midline shift among the patients with neurological worsening

No.	Stroke types	Lesion side	NPi before neurological worsening (right/left)	NPi after neurological worsening (right/left)	Change of midline shift (mm)
1	Ischemic stroke	Right	4.3/4.4	0.0/4.0	12.7 → 17.5
2	Ischemic stroke	Right	4.2/4.0	1.9/1.2	10.7 → 14.5
3	Ischemic stroke	Right	4.9/4.9	3.6/3.6	4.2 → 8.2
4	Ischemic stroke	Left	4.5/4.7	4.4/4.1	2.1 → 13.3
5	Ischemic stroke	Bilateral	4.1/4.2	3.4/3.2	3.4 → 9.0
6	Hemorrhagic stroke	Left	3.9/4.0	2.0/2.7	0 → 1.9
7	Ischemic stroke	Right	4.0/4.1	2.5/3.0	0 → 9.0
8	Ischemic stroke	Right	4.5/4.2	4.1/4.1	4.5 → 11.7
9	Ischemic stroke	Bilateral	4.0/4.0	3.1/4.0	16.2 → 17.6
10	Ischemic stroke	Right	0.9/4.1	0/0	5.4 → 6.5

*Midline shift was assessed by measuring the distance from the midline to the septum pellucidum using brain CT
NPi neurological pupil index

- This study showed that a sudden drop of NPi value below 2.8 was always associated with neurological worsening, regardless of the side of the lesion.
- A percentage decrease in NPi by 30% as compared to the immediate previous assessment was associated with neurological worsening in patients suffering large hemispheric strokes.
- In this study, 80% of the patients of the neurological worsening group had a significant decrease in the NPi value, accompanied by an aggravation of the midline shift on brain CT.

Medication effects on the pupillary light reflex

- Several kinds of medications including opioids, sedative drugs are frequently used in the neurological ICU.
- Those drugs affect pupil size and reactivity during NICU hospitalization.
- NM blockers preserve pupil light reflex.
- Lack of studies and evidences about the medication effects on the PLR
- However, quantitative pupillometry should be interpreted in context with a consideration of medication influences.

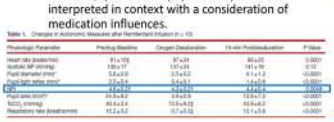


Table 2. Summary of Medication Effects on the Pupillary Light Reflex.

Medication	Dose	Effect on Pupil Size	Effect on Pupillary Dynamics
Remifentanil[39]	Titrated to respiratory depression	Miosis	Reduced PLR*
Vecuronium[19]	0.15 mg/kg	None	None
Diphenhydramine[38]	75 mg	Miosis	None
Diazepam[38]	10 mg	None	None
Propofol[38]	0.3-0.7 mg/kg bolus; 200-800 mg maintenance	Miosis	Reduced CV
Barbiturate[40]	Titrated to burst suppression	Not reported	Reduced CV
Ondansetron[41]	0.13 mg/kg	None	None
Metoclopramide[42]	0.5 mg/kg	Miosis	Reduced PRD
Droperidol[42]	0.02 mg/kg	Miosis	Reduced PRD

Abbreviations: CV, constriction velocity; NPi, Neurological Pupil index; PLR, pupillary light reflex; PRD, pupillary reflex dilation.
*Measured by change in pupil size in millimeters and NPi.

J Intensive Care Med. 2019 Oct 10:885066619881124
Anesthesiology 2014; 121:1037-44

Case

- 55세 남자
- HCC 수술 후 중환자실 입원 치료 중 Rt pupil dilatation 으로 emergency contact
- Headache (-) eyeball pain (-)
- Neurological examination
  - alert and follow command: OK
  - EOM: OK
  - PLR 이외 다른 검진 모두 정상

Unilateral dilated pupil and decreased pupil reactivity :emergent finding – ischemic stroke, hemorrhagic stroke, tumor bleeding with uncal herniation

Conclusions

- The PLR has been established as an important clinical tool in evaluating wide variety of neurological conditions.
- Quantitative pupillometry could minimize possible inter-observer variability in the pupillary evaluation.
- The advent of automated pupillometry has provided not only more reliable and quantitative data but also adds neurological status monitoring including post-CA prognostication, ICP monitoring, outcome, and neurological worsening in NeuroICU.
- The PLR is affected by numerous medical conditions and medications in ICU.