Summary of Clinical Paper:

Oddo M, Sandroni C, Citerio G, Miroz JP, Horn J, Rundgren M, Cariou A, Payen JF, Storm C, Stammet P, Taccone FS: **Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: An international prospective multicenter double-blinded study.** Intensive Care Med, 44(12):2102-2111, 2018. DOI: 10.1007/s00134-018-5448-6

Background

- This large, multicenter study is the first of its kind to assess the prognostic value of pupillary reactivity using Neurological Pupil index (NPi) in the acute phase of post- anoxic coma in patients following cardiac arrest (CA).

- *Intensive Care Medicine* is the official journal of the European Society of **Intensive Care Medicine** (ESICM) and the European Society of Paediatric and Neonatal Intensive Care; it is a highly respected medical journal.

- This is a prospective, international multicenter study taking place at 10 centers across 8 European countries involving the following 11 clinicians:

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Aim of the Study

- The study had two primary objectives:
  1) to assess the ability of quantitative pupillometry [using the Neurological Pupil index (NPi)] **to predict an unfavorable neurological outcome 3 months after cardiac arrest** (CA).

  2) to evaluate **whether NPi can help discriminate** between **good outcome** (full recovery or moderate disability) vs. **unfavorable outcome** (severe disability, vegetative state or death).

- The study involved 456 comatose patients with a GCS of ≤ 6 resuscitated post-cardiac arrest (CA) and treated with Targeted Temperature Management (TTM).

Methods

- Pupil measurements were performed from day 1 to day 3 after CA. Quantitative NPi and standard manual pupillary light reflex (sPLR) were blindly recorded in parallel from day 1 to 3 following CA, (the measurements were not disclosed to clinicians or outcome assessors).
- The primary study endpoint was to compare the prognostic value of NPi versus sPLR to predict 3-month Cerebral Performance Category (CPC) Scale readings at 3-months, paired as **favorable** (CPC 1–2: full recovery moderate disability) versus **unfavorable** outcome (CPC 3–5: severe disability, vegetative state, or death).
- An additional endpoint included evaluating the prognostic value of NPi when used in combination with SSEP (somatosensory evoked potentials), a noninvasively test that assesses somatosensory function by measuring the electrical activity of the brain. SSEP is used post-resuscitation for prognostication following CA. An additional finding in this study showed that adding NPi to SSEP improved the sensitivity to predict an unfavorable outcome in patients with CA, while providing equal 100% specificity (the combo improved the results even more).

Note: It is important to understand that clinical "prognostication", or "prediction of patient outcome", is done by the clinical team to help inform and prepare the patient and their family for the post-discharge period and assist them in planning for the subsequent patient care that will be required.

Results

- The predictive value for an unfavorable outcome of **NPi was superior** to sPLR at every time-point in the test.
- The most striking results were:
  - **NPi had 100% PPV**, meaning 100% of patients that had even one NPi reading of ≤ 2 had an unfavorable outcome.

- **NPi had 100% specificity**, meaning all patients (100%) with a good outcome had ZERO NPi readings of ≤ 2.

- In summary, there were four main results:

	RESULT	WHAT DOES THIS MEAN?
RESULT 1	51% negative predictive value (NPV), meaning that **51% of the patients that NEVER had occurrence of NPi ≤ 2 had a good outcome**	➔ A "good" NPi (> 2) does not necessarily mean a good outcome (CPC 1-2).
RESULT 2	100% positive predictive value (PPV), meaning that **ALL (100%) the patients that had at least one occurrence of NPi ≤ 2 had unfavorable outcome**	➔ A "bad" NPi (≤ 2) **ALWAYS** means unfavorable, or "bad" outcome (CPC 3-5).
RESULT 3	100% specificity meaning that **ALL patients with a good outcome NEVER had occurrence of NPi ≤ 2**	➔ **ALL** (100%) patients with a good outcome had "good" NPi (> 2).
RESULT 4	32% sensitivity meaning that **only 32% of those patients with unfavorable outcome had occurrence of NPi ≤ 2**	➔ Not all patients with an unfavorable outcome had "bad" NPi (≤ 2).

Conclusions

There are three main conclusions that speak to the clinical and prognostic value of NPi:

- A quantitative measurement of the pupillary function (NPi), using automated infrared pupillometry, in patients who are comatose following resuscitation post- CA, predicted an unfavorable neurological outcome at 3 months more accurately than standard pupillary examination using a manual device.

- The predictive value for an unfavorable outcome of **NPi was superior** to that of sPLR at each time-point tested. An NPI ≤ 2 between day 1 and day 3 following hospital admission was 100% specific to predict (able to predict 100% of the time) an unfavorable 3-month neurological outcome and provided greater prognostic performance than standard manual pupillary light reactivity.

- The data further suggest that using a prognostic approach that combines NPi with somatosensory evoked potentials (SSEP) improved the sensitivity to predict an unfavorable outcome in patients post-CA, while providing equal 100% specificity.

Questions/ Answers

Why is this an important study?

This study is a very big deal because it is the first of its kind to assess the prognostic value of the Neurological Pupil index (NPi) in a specific group of patients within a specific clinical diagnosis. The quality of the science behind it is extensive, the institutions and clinicians involved are highly regarded in Europe and in the US, and the peer-reviewed journal, *Intensive Care Medicine*, is widely acclaimed. It's a win for NeurOptics all the way around.

Why did the study establish NPi ≤ 2 as the criteria threshold, vs NPi < 3?

NPi ≤ 2 proved to be the measurement range achieving the best result. The authors found that a cut-off for NPi of ≤ 2, occurring any time between day 1 and day 3, provided maximum sensitivity [32%] to predict unfavorable outcome, while achieving 100% specificity and 100% positive predictive value (0% false-positive rate).

What is the Cerebral Performance Category (CPC) Scale, and why was that used as a metric to evaluate outcome at 3 months? And, why is it 3 months?

The Cerebral Performance Category (CPC) Scale is an assessment scale of neurologic functioning, represented below. It is frequently used as an adjunct to the Glascow Coma Scale (GCS), and is widely used to evaluate post-discharge patient outcomes. A 90-day post-discharge time period is a typical metric that clinicians use to predict, and subsequently evaluate, a patient's long-term health status.

Cerebral Performance Category (CPC) Scale

Favorable	CPC 1	Full recovery (A return to normal cerebral function and normal living)
	CPC 2	Moderate disability, returned home (Cerebral disability but sufficient function for independent activities of daily living
Unfavorable	CPC 3	Severe disability, at a rehab facility (limited cognition, inability to carry out independent existence)
	CPC 4	Vegetative State (coma)
	CPC 5	Death (brain death)

What is positive predictive value (PPV), and why is it important in this study?

The positive predictive value (PPV) is a statistic term that expresses the % probability of a positive result. You cannot get any better than 100% PPV.

In this study, the 100% PPV result indicated that any patient measuring an NPi ≤ 2, performed between day 1 and day 3 following hospital admission, was "100% specific to predict" (able to predict 100% of the time) an unfavorable 3-month neurological outcome. This indicates that qPLR (quantitative pupillometry), and specifically the use of NPi, provides greater prognostic performance than standard manual pupillary light reactivity.

What is Specificity vs Sensitivity, and why does anybody care?

Sensitivity and **specificity** are statistical measures of the performance of a study, and clinicians look at these as indicators of the clinical study performance:

- **Sensitivity** (aka: "**true positive rate"**) measures the proportion of actual positives that are correctly identified as such (e.g., the percentage of sick people who are correctly identified as having the condition).

- **Specificity** (aka: "**true negative rate"**) measures the proportion of actual negatives that are correctly identified as such (e.g., the percentage of healthy people who are correctly identified as not having the condition).

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Attached is the study. Please let me know what questions you have.

Kath