Correlation Between Electroencephalography and Automated Pupillometry in Critically Ill Patients: A Pilot Study

Sania Hasan, MD,*† Lorenzo Peluso, MD,* Lorenzo Ferlini, MD,† Benoît Legros, MD, PhD,† Lorenzo Calabro, MD,* Mauro Oddo, MD,‡ Jacques Creteur, MD, PhD,* Jean-Louis Vincent, MD, PhD,* Nicolas Gaspard, MD, PhD,* and Fabio S. Taccone, MD, PhD*

**Background:** Electroencephalography (EEG) is widely used in the monitoring of critically ill comatose patients, but its interpretation is not straightforward. The aim of this study was to evaluate whether there is a correlation between EEG background pattern/reactivity to stimuli and automated pupillometry in critically ill patients.

**Methods:** Prospective assessment of pupillary changes to light stimulation was obtained using an automated pupillometry (NeuroLight Algiscan, ID-MED, Marseille, France) in 60 adult patients monitored with continuous EEG. The degree of encephalopathy and EEG reactivity were scored by 3 independent neurophysiologists blinded to the patient's history. The median values of baseline pupil size, pupillary constriction, constriction velocity, and latency were collected for both eyes. To assess sensitivity and specificity, we calculated areas under the receiver-operating characteristic curve.

**Results:** The degree of encephalopathy assessed by EEG was categorized as mild (42%), moderate (37%), severe (10%) or suppression-burst/suppression (12%); a total of 47/60 EEG recordings were classified as “reactive.” There was a significant difference in pupillary size, constriction rate, and constriction velocity, but not latency, among the different EEG categories of encephalopathy. Similarly, reactive EEG tracings were associated with greater pupil size, pupillary constriction rate, and constriction velocity compared with nonreactive recordings; there were no significant differences in latency. Pupillary constriction rate values had an area under the curve of 0.83 to predict the presence of severe encephalopathy or suppression-burst/suppression, with a pupillary constriction rate of < 20% having a sensitivity of 85% and a specificity of 79%.

**Conclusions:** Automated pupillometry can contribute to the assessment of cerebral dysfunction in critically ill patients.

**Key Words:** EEG, automated pupillometry, brain dysfunction

(*J Neurosurg Anesthesiol 2019;00:000-000*)

**Neurological dysfunction in critically ill patients can be the result of a variety of structural, metabolic, infectious, or toxic causes and is associated with significant morbidity and mortality.** However, brain dysfunction can be difficult to assess because clinical neurological examination is often limited by the use of sedatives or concomitant systemic complications. As such, several invasive and noninvasive tools have been developed to assess brain perfusion, oxygenation, metabolism, and function.

Electroencephalography (EEG) is one of the most commonly used monitoring tools in the ICU. In particular, an EEG is used to guide the management of status epilepticus, to monitor and predict the severity of brain injury in patients resuscitated from cardiac arrest, and to exclude nonconvulsive seizures in patients with unexplained neurological impairment. Also, in some countries, isoelectric EEG recordings are used to confirm the diagnosis of brain death. Continuous EEG monitoring (cEEG) requires an experienced neurophysiologist for its proper interpretation, and it is also highly time-consuming and resource intensive to perform. Moreover, the EEG recordings are very sensitive to changes in brain activity, to different intracranial and extracranial diseases and to sedative drugs. If appropriately trained, intensivists can
evaluate basic or quantitative EEG data (eg, depth of sedation, symmetry between the hemispheres, recognition of seizures, or artifacts), but this is not widely performed. Surrogates of EEG-derived information could therefore be useful to identify patients “at-risk” of EEG abnormalities, and in whom earlier EEG recording and close monitoring might be beneficial.

Pupillary examination provides information on brainstem integrity, cortical activity, or the function of the autonomic nervous system. Clinical assessment of pupillary size and light reactivity shows substantial interobserver variability, in particular for small pupils and dark irises, and is hindered by lack of adequate descriptive terminology (eg, brisk, sluggish, or nonreactive pupil). Automated pupillometry produces a quantitative and reliable assessment of pupillary size and degree of constriction or dilation to light or painful stimuli. No data comparing EEG and automated pupillometry findings have been published.

The aim of this study was to evaluate whether there is a correlation between the 2 main EEG findings (ie, background pattern and reactivity to stimuli) and automated pupillometry-derived parameters in ICU patients.

METHODS

This was a prospective study including adult ICU patients requiring cEEG monitoring between November 6, 2017 and March 26, 2018. The decision to initiate cEEG monitoring was made by the attending ICU physician in collaboration with neurophysiologists. Patients with known pupillary abnormalities, multiple sclerosis, ocular surgery, or severe periorbital edema limiting pupillary assessment were not considered. The local Ethics Committee approved the study (P2018/308), with waiver of informed consent because cEEG and automated pupillometry are standard monitoring modalities in patients with neurological dysfunction in our department.

Automated Pupillometry and EEG Assessment

Automated pupillometry was performed by 2 operators (S.H. and L.P.) with a NeuroLightAlgiscan (ID-MED, Marseille, France) according to standard methodology using a burst of light emitted by the device (Supplementary Methods 1, Supplemental Digital Content 1, http://links.lww.com/JNA/A183). Measurements were made in both eyes and the mean value used for comparison with EEG findings: baseline pupil size (mm), pupillary constriction rate (difference between baseline and poststimulation pupil size expressed as % of constriction from baseline value), constriction velocity (mm/s) and latency (ms). Anisocoria was defined as a difference of at least 1.0 mm between the 2 eyes. In comatose patients, an electrical stimulation with variable intensity (increasing from 10 mA to a maximum of 60 mA) was applied to the left and right forearm using 2 electrodes linked to the automated pupillometer as part of routine pain assessment in unconscious patients in our unit. Baseline pupil size (mm), pupillary dilation to pain (ie, the difference between poststimulation and baseline pupil size, expressed as %) and pupillary pain index (PPI) were obtained. PPI assigns a score from 1 (pupillary dilation <5% to the maximal stimulation intensity) to 10 (pupillary dilation >13% with 10 mA stimulus).

A 20-min 21 electrode EEG epoch recording around the time of the automated pupillometry assessment was assessed by 3 independent neurophysiologists. The EEG background pattern was classified into 1 of the 4 categories of encephalopathy using a modified Synek scale (Supplementary Methods 2, Supplemental Digital Content 2, http://links.lww.com/JNA/A184). The presence of EEG changes to external stimulation (name call for awake patients and painful stimuli for unconscious patients), that is, EEG “reactivity,” was also assessed, and the EEG background pattern categorized as “reactive,” “nonreactive,” or “unclear.”

Data Collection

Patient demographics; medical history; and clinical, respiratory, and biological data on the day of the study were collected. The severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score and conscious level of the day of the study using the Glasgow Coma Scale (GCS) score. Reasons for cEEG recording and time from ICU admission and cEEG initiation to automated pupillometry assessment were also collected. The use of drugs that might interfere with pupillary constriction (ie, opioids, sedatives, or barbiturates) and antiepileptic drugs was noted. As this was an exploratory study, no additional adjustment of data analyses to reduce the potential sources of bias was performed.

Statistical Analysis

Statistical analyses were performed using Matlab (The MathWorks, Natick, MA). Interobserver agreement on the interpretation of EEG encephalopathy severity and variability, and EEG reactivity to automated pupillometry, among the 3 neurophysiologists was quantified using the Gwet multirater agreement coefficient AC1 (Supplementary Methods 3, Supplemental Digital Content 3, http://links.lww.com/JNA/A185) and percentage of agreement. The presence of an association between EEG category of encephalopathy and automated pupillometry-derived parameters was evaluated using a Kruskal-Wallis test. The discriminative ability of automated pupillometry variables to predict severe encephalopathy/suppression-burst suppression or a reactive EEG was evaluated using receiver-operating characteristic curves with the corresponding area under the curve (AUC) and related sensitivity and specificity. The data are presented as median (25th to 75th percentiles) or count (%), and a P-value <0.05 was considered significant. In the absence of any previous data on this topic, we included a “convenience” sample, with no specific sample size calculation performed.

RESULTS

A total of 130 patients underwent cEEG during the study period; 3 were not eligible for inclusion in the study (previous ocular surgery), 25 were excluded because they were monitored at the weekend (pupillometry assessment
not clearly noted in the EEG monitoring system), and 42 were excluded because the automated pupillometry operator was not available. A total of 60 patients were included in the final analysis, and there were no missing data (Supplementary Fig. 1, Supplemental Digital Content 4, http://links.lww.com/JNA/A186). The characteristics of the study population are shown in Supplementary Table 1 (Supplemental Digital Content 5, http://links.lww.com/JNA/A187). Most patients (n = 41, 68%) were admitted with a primary neurological diagnosis. 68% of the patients were receiving opioids, in particular morphine (42%) or sufentanil (32%), and 38% were receiving propofol or midazolam on the day of the study. ICU mortality was 40% (Supplementary Table 2, Supplemental Digital Content 6, http://links.lww.com/JNA/A188).

**EEG Interpretation and Interobserver Reliability**

Forty (67%) of the EEG recordings were categorized identically by all the 3 neurophysiologists, and 20 (33%; all for mild/moderate encephalopathy) by 2 of the neurophysiologists. The agreement for encephalopathy classification was 95% and Gwet coefficient was 0.88; the EEGs were categorized as mild (n = 25, 42%), moderate (n = 22, 37%), severe (n = 6, 10%), or suppression-burst/suppression (n = 7, 12%) encephalopathy. Forty-seven of the 60 (78%) EEG recordings were categorized in the con- 

cclusion of the development and severity of encephalopathy (n = 16) had greater pupillary size (3.2 [2.5 to 3.7] vs. 1.9 [1.8-3.2] mm; P = 0.048), pupillary dilation rate (21 [10 to 28] vs. 7 [confidence interval, 1-13%]; P = 0.01) and PPI (5.7 [2.2 to 6.9] vs. 1.8 [1.0 to 3.3]; P = 0.01) compared with those with severe encephalopathy or suppression-burst/suppression. Similar results were seen for EEG reactivity (Supplementary Fig. 3, Supplemental Digital Content 8, http://links.lww.com/JNA/A190).

**Correlation Between EEG Encephalopathy and Pupillometry Variables With Light Stimulation**

There was a correlation between GCS score on the day of the study and both pupillary constriction rate and constriction velocity (Supplementary Fig. 4, Supplemental Digital Content 9, http://links.lww.com/JNA/A191).

**DISCUSSION**

In this study, pupillary size, constriction rate, and constriction velocity were correlated with the degree of an EEG-defined encephalopathy and with an EEG reactivity to external stimuli. In particular, the more severe the encephalopathy the less marked was the quantitative pupillary reflex to light. Automated pupillometry variables were also correlated with clinical status, as assessed by the GCS. These findings suggest that automated pupillometry can be used as a tool to identify critically ill patients at-risk of EEG-defined severe encephalopathy.

Pupillary size is controlled by the balance between sympathetic and parasympathetic systems integrated at the level of the midbrain, and by neuronal activity in the locus coeruleus, colliculi, and cingulate cortex.9 Multiple neurotransmitter systems have been identified in the control of cortical activity which may also affect pupillary size.11 in particular acetylcholine and norepinephrine.16 Cholinergic innervation of the cortex is provided by the basal forebrain and noradrenergic innervation by the locus coeruleus;17 both these systems are known to influence pupillary size. It is likely because of these common pathways that we found a correlation between abnormalities in pupillary function and pathologic EEG findings in our study. Although this might appear obvious, as both are established monitoring modalities of neurological function in critically ill patients, the use of automated pupillometry and EEG in future studies might expand our understanding of the development and severity of encephalopathies, and the potential for these modalities to assess encephalopathy severity and prognosis.

Correlation of baseline pupillary size, pupillary constriction rate, and velocity with EEG background activity also involves a correlation with an EEG reactivity to external stimuli, a parameter known to be a predictor of long-term outcome in traumatic brain injury patients and in comatose patients resuscitated after cardiac arrest and treated with targeted temperature management.15,18 Reduced variability of EEG alpha activity has also been identified as a sensitive and specific prognostic factor in patients with moderate to severe traumatic brain injury within 3 days after injury.19 Despite this correlation with EEG reactivity, we found that EEG reactivity was not
influenced by pain or light stimulation in our study; only 4 EEG recordings were classified as “reactive” after automated pupillometry assessment. However, no previous study has assessed the correlation between the EEG and pupillometry findings.

In our study there was considerable agreement among specialist neurophysiologists in the classification of EEG reactivity, and very good agreement in the EEG classification of encephalopathy. In previous studies, agreement among experts on the classification of EEG reactivity has varied from 53% to 83%. A recent study investigating 103 EEGs from comatose patients with postanoxic brain injury reported substantial agreement only for highly malignant EEG patterns and poor agreement in the assessment of unreactive pupils.20,21 The higher level of agreement in our study might be explained by the fact that all the neurophysiologists work in the same institution and have likely developed similar methods for evaluating EEGs in their daily practice. However, no instruction or training was provided to the neurophysiologists concerning EEG interpretation in this study.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.
Further, to avoid bias in measurement, interpretation was performed blindly; the neurophysiologists were not aware of the clinical status of the individual patients.

This study has several limitations. First, the number of patients was small, in particular for comparison of EEG and automated pupillometry response to pain stimuli. The statistical analysis was thus limited, and no additional associative evaluations could be performed. Larger, multicenter trials are needed to better understand the relationship between EEG and automated pupillary assessment in critically ill patients. Also, inter-rater agreement for EEG assessment was based on 2 of 3 neurophysiologists in 33% of the recordings, although this was only for EEGs showing mild/moderate encephalopathy. Second, we did not specifically discriminate between primary and “sedation-induced” encephalopathy, and some pharmacologic agents affecting the sympathetic and parasympathetic nervous systems can alter pupil size. As such it is difficult to separate the effects of structural brain damage, increased intracranial pressure, or pharmacological therapy on the pupillary alterations in this study. Nevertheless, this study did not aim to evaluate these relationships, but rather to describe any association between EEG and pupillometry findings. Opioids are known to induce pupillary constriction, and propofol can decrease the variability in pupillary diameters and constriction velocity. We did not adjust our findings according to the use and/or total dose of sedatives or analgesics, and this might have been useful to eliminate potential bias. However, the use of automated pupillometry and EEG is of particular interest in patients in whom clinical examination is unreliable (such as those receiving sedation) so we did not consider further statistical correction to be necessary. Third, age is another important factor that can influence pupillary constriction; resting pupil size progressively decreases after the fourth decade of life. Fourth, automated pupillometry does not provide a continuous measurement of pupillary activity, and further research is needed to determine the value of serial pupillometry readings. Also, pupillary assessment using automated pupillometry was not a part of clinical decision algorithm at the time of this study; as such, the role of the combination of pupillometry and EEG findings to guide therapeutic decision could not be evaluated. Fifth, the assessment of latency using automated pupillometry has some limitations because the device cannot capture the signal at a high enough frequency; this might explain the lack of correlation between EEG findings and pupillary latency in our study. Sixth, we did not assess the level of training and learning curve to minimize interobserver variability in pupillary diameters and constriction velocity.
ability for automated pupillometry assessments; however, high interdevice reliability of automated pupillometry between 2 practitioners has previously been described in critically ill patients.25 Seventh, the ICU mortality was high in this study, which may suggest a selection bias toward severely ill patients. Another limitation was related to the relatively limited analytics of the pupillometer used in this study; some competitor devices provide additional information (eg, Neurologic Pupil Index). Finally, using mean values from both pupils risks oversimplifying underlying brain dysfunction; focal cerebral injury may be associated with significant differences between the eyes.

CONCLUSIONS
This study shows a significant association between the degree of encephalopathy determined by EEG and quantitative automated pupillometry measures. Automated pupillometry may identify patients at high-risk for nonreactive EEG.

REFERENCES