



# Pupillometry in critically ill patients with COVID-19: a prospective study

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Received: 24 July 2020 / Accepted: 28 September 2020 / Published online: 7 October 2020  
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**Keywords** Portable pupillometry · Autonomic nervous system · COVID-19

Dear Editor,

Since December 2019 severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread over the entire world, causing the coronavirus disease 2019 (COVID-19) pandemic [1]. COVID-19 is characterized by an excessive inflammatory response [2] that could theoretically affect the pupillary light reflex (PLR) by the following mechanism: inflammatory molecules, such as cytokines, are detected by the afferent vagus nerve fibers, which terminate at the solitary nucleus; the solitary nucleus projects into the locus coeruleus, the brainstem nucleus which controls autonomic function and is the main source of norepinephrine in the brain. Locus coeruleus activation is correlated to increased pupil size, but the associated physiological mechanisms have

not yet been elucidated [3]. Locus coeruleus activation also attenuates pupillary constriction via inhibitory projections to the Edinger–Westphal nucleus [4]. It is therefore plausible to expect that patients with COVID-19 have increased pupil size and decreased pupillary response to light compared to other patients with respiratory failure. Demonstrating such differences would be of clinical value because it would provide evidence for the application of pupillometry as a marker of autonomic nervous system (ANS) involvement in COVID-19 and potentially in other infectious diseases [5].

To investigate this hypothesis we measured the various parameters of the PLR of critically ill patients with COVID-19 and compared these parameters with those of patients with respiratory failure of different etiology. The study took place between 20 February and 27 April 2020, in the Intensive Care Unit (ICU) Department of Evangelismos General Hospital, Athens, Greece. The study was approved by the Scientific and Ethics Committee of Evangelismos Hospital, and written informed consent was obtained from all study participants or from their next of kin.

The inclusion criteria were: age > 18 years; admission to hospital with respiratory failure requiring mechanical ventilation for > 48 h; and informed consent from the patient or patient's next of kin. Exclusion criteria were: history, evidence or suspicion of primary neurological injury; presence of agitation or delirium; known ocular disease; disease severity that rendered treatment futile; the presence of shock requiring treatment with high-dose vasoconstrictors (dopamine > 15 µg/kg/min, or epinephrine > 0.1 µg/kg/min, or norepinephrine > 0.1 µg/kg/min) [6]; pregnancy; and β-blocker or other anti-hypertensive drug administration at the time of evaluation. To limit the variability caused by different levels of sedation in the study population [7], we assessed the depth of sedation with the Ramsay Sedation Scale [8]. Patients who were deeply sedated (Ramsay

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**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s10286-020-00737-7>) contains supplementary material, which is available to authorized users.

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score 6) and patients who were awake (Ramsay score 2) and not on any sedatives for at least 1 h prior to the initial assessment were included in the study. Patients with Ramsay scores ranging from 3 to 5 and patients on low-dose remifentanyl, dexmedetomidine or clonidine at the time of the initial assessment were scheduled to be re-assessed the following day. COVID-19 status was based upon positive SARS-CoV-2 real-time reverse transcriptase-PCR assay of nasopharyngeal swab specimens. For the purpose of this analysis, the patients were divided into four groups, as shown in Table 1 and in the study flowchart in the Electronic Supplementary Material (ESM).

We assessed the PLR using the NP200 pupillometer system (NeuroOptics, Laguna Hills, CA, USA) according to the manufacturer's instructions [9]. Three measurements were taken for each participant within a 30-min interval, and the average of these three measurements was used for statistical analysis. The variables recorded included the neurological pupil index (NPi), maximum pupil diameter before constriction (Size), minimum pupil diameter at peak constriction (Min), percentage of change of the pupil diameter during constriction [ $\Delta$ Size (%)], pupil latency (LAT; i.e., the time-of-onset of constriction following initiation of the light stimulus), average constriction velocity (CV), maximum constriction velocity (MCV) and dilation velocity (DV). All measurements were performed under dim light conditions (5–11 lx) measured by a lux-meter (Peakmeter PM6612). Since patients with known or likely neural injury were excluded, left and right eye PLR measurements were pooled together.

We used non-parametric methods for statistical testing using IBM SPSS statistics version 25 (IBM Corp., Armonk,

NY, USA). Statistical significance was set at  $p < 0.05$ . We included 41 patients in the analysis, 18 of whom were diagnosed with COVID-19 and 23 of whom were diagnosed with respiratory failure of a different etiology. The demographic and clinical characteristics of the study population are given in detail in the ESM. A summary of the PLR measurements and statistical comparisons between groups are given in Table 1. Data pertaining to individual patients are graphically provided in the ESM. There were no significant differences in the PLR parameters between COVID-19-positive (+) and COVID-19-negative (–) patients. To assess the power of these comparisons we considered alternative hypotheses based on previously published data from PLR assessment in patients with ANS dysfunction [10]. The power for the comparisons of the MCV, assuming the alternative hypothesis that MCV is at least 34.3% lower in patients with COVID-19, was 79.5% for sedated and 82.9% for awake patients. The effect of sedatives was far more significant than the COVID-19 status in our sample, even though not all PLR variables were equally affected by sedation. More precisely, it was pupil size, and variables that depend on pupil size [Min,  $\Delta$ size (%), CV, MCV] that were affected, as was DV. The NPi, an indicator of elevated intracranial pressure [9], did not differ significantly among the four groups. This was expected, since patients with diagnosed or likely primary neural injury were excluded.

The absence of significant differences in the PLR between the COVID-19 (+) and COVID-19 (–) patients can be attributed to several possible reasons. One possibility is that sympathetic activation is not actually different in SARS-CoV-2 infection compared to other causes of respiratory failure. Another is that even though COVID-19 affects the ANS,

**Table 1** Pupillometry measurements in the different patient groups

Variable	Sedated (Ramsay score 6)		Awake (Ramsay score 2)	
	Group a: COVID-19 negative ( $n = 14$ )	Group b: COVID-19 positive (+) ( $n = 6$ )	Group c: COVID-19 negative ( $n = 9$ )	Group d: COVID-19 positive ( $n = 12$ )
NPi	4.52 (3.98–4.70)	4.44 (4.18–4.61)	4.53 (4.45–4.55)	4.64 (4.39–4.71)
Size	2.26 (1.99–2.72)**	2.10 (2.05–2.63) <sup>†</sup>	3.69 (3.18–4.53)**	3.50 (3.06–4.20) <sup>†</sup>
Min	1.87 (1.66–2.32)*	1.82 (1.73–2.19)	2.60 (2.27–2.73)*	2.33 (2.05–2.80)
$\Delta$ Size (%)	15.7 (12.9–20.0)**	18.2 (15.6–20.1) <sup>††</sup>	30.7 (26.5–32.8)**	35.0 (30.4–37.3) <sup>††</sup>
CV	0.82 (0.76–1.05)**	0.96 (0.80–1.07) <sup>††</sup>	1.95 (1.55–2.32)**	2.29 (1.93–2.54) <sup>††</sup>
MCV	1.36 (1.11–1.52)**	1.39 (1.31–1.59) <sup>††</sup>	2.98 (2.89–3.68)**	3.50 (3.27–4.08) <sup>††</sup>
DV	0.37 (0.29–0.45)**	0.43 (0.32–0.52) <sup>††</sup>	1.03 (0.84–1.17)**	1.03 (0.91–1.17) <sup>††</sup>
Latency	0.26 (0.24–0.28)	0.29 (0.25–0.30)	0.24 (0.23–0.25)	0.25 (0.23–0.26)

All values in table are presented as median with the interquartile range in parentheses

COVID-19 Coronavirus Disease-19, NPi neurological pupil index, Min minimum pupil size,  $\Delta$ Size (%) (Size–Min)/Size  $\times$  100%, CV constriction velocity, MCV maximum constriction velocity, DV dilation velocity

\*Significant difference at  $p < 0.05$  (Mann–Whitney  $U$  test) between groups a and c; \*\*significant difference at  $p < 0.001$  (Mann–Whitney  $U$  test) between groups a and c; <sup>†</sup>significant difference at  $p < 0.05$  (Mann–Whitney  $U$  test) between groups b and d; <sup>††</sup>significant difference at  $p < 0.001$  (Mann–Whitney  $U$  test) between groups b and d

this effect is attenuated in the ICU population by ICU-related interventions, such as the administration of anesthetics, analgesics and inotropic medications that may have a prolonged effect. A limitation of our study is its small sample size, due to the small number of ICU admissions with COVID-19 in Greece during the study period. Furthermore, our measurements were not blinded to the examiners, as this was not feasible given the nature of the study question.

In conclusion, PLR measurements were not significantly different between ICU patients treated for COVID-19 and patients with respiratory failure of different cause. Further prospective studies are needed to investigate whether such differences are present at earlier or later stages of the disease.

**Funding** No funding was received for this work.

**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study was approved by the scientific and Ethics committee of Evangelismos Hospital.

**Informed consent** Written informed consent was obtained from all study participants or from their next of kin.

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