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## Competing Interests

The authors declare no competing interests.

**Andreas Güldner, M.D., Thomas Kiss, M.D., Ary Serpa Neto, M.D., M.Sc., Sabine N. T. Hemmes, M.D., Jaime Canet, M.D., Ph.D., Peter M. Spieth, M.D., Patricia R. M. Rocco, M.D., Ph.D., Marcus J. Schultz, M.D., Ph.D., Paolo Pelosi, M.D., F.E.R.S., Marcelo Gama de Abreu, M.D., M.Sc., Ph.D., D.E.S.A.** University Hospital Carl Gustav Carus, Dresden, Germany (M.G.d.A.). mgabreu@uniklinikum-dresden.de

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## Limitations of the Pupillary Reflex: Do the Eyes Have It?

To the Editor:

We read the article by Guglielminotti *et al.*<sup>1</sup> and the accompanying editorial by Larson and Gupta<sup>2</sup> with great interest. Guglielminotti *et al.* used pupillary dilation reflex amplitude in response to a standardized noxious test to predict movement upon surgical stimulation in young (28 ± 6 yr old) women without known diabetes who were receiving general total intravenous anesthesia. In the accompanying editorial,

Larson and Gupta<sup>2</sup> stated that “rare syndromes” such as diabetic neuropathy could interfere with the accuracy of this type of testing.

By using commonly accepted hemoglobin A1C as the criterion, it is shown that 9.6% of Americans older than 20 yr and 21.1% of Americans older than 65 yr have diabetes.<sup>3</sup> These patients are more likely to have a surgical procedure than nondiabetic patients.<sup>4</sup> Furthermore, as many as 50% of patients with diabetes will need a surgical procedure in their lifetime.<sup>5</sup> Fulk *et al.*<sup>6</sup> examined non-insulin-dependent patients with diabetes for sympathetic denervation of the iris dilator. They showed that “pupillary neuropathy can develop in persons with diabetes, often before the other complications of diabetes become manifest.” Furthermore, a study of children with diabetes found that abnormal pupillary adaptation is common and progressive over time and may be an indicator of early tissue damage.<sup>7</sup> Pittasch *et al.*<sup>8</sup> examined pupils of patients with type 1 diabetes and demonstrated that pupillary sympathetic denervation occurs in these patients. Clearly, even those with early-stage diabetes may have abnormal pupillary responses, thus limiting this technology in many of our patients.

Guglielminotti *et al.*<sup>1</sup> included only young women, but we know that the autonomic nervous system changes with advancing age and with those changes come reduced pupillary responses. Bitsios *et al.*<sup>9</sup> found that the amplitude and velocity of the darkness reflex were reduced and the time of recovery of the light reflex was increased (both signs of decreased sympathetic outflow) in the elderly.

Given that a large number of surgical patients will have diabetes and/or advanced age, potential factors associated with pupillary dysfunction, we caution readers that these two comorbidities could limit the applicability of pupillary dilation reflex amplitude to a generalized patient population.

## Competing Interests

The authors declare no competing interests.

**Koffi M. Klla, M.D., Douglas B. Coursin, M.D., Mark J. Rice, M.D.** Vanderbilt Medical Center, Nashville, Tennessee (K.M.K.). koffi.m.klla@vanderbilt.edu

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### In Reply:

We thank Kla *et al.* for their interest and comments on our recent publication in *ANESTHESIOLOGY*.<sup>1</sup> They raise concerns about the generalizability of the results of our study conducted in young and healthy patients, considering (1) the prevalence of elderly or diabetic patients in surgical patients and (2) the pupillary autonomic dysfunction associated with these two conditions.

Elderly patients make up a significant proportion of the surgical population in the United States and worldwide. According to the Centers for Disease Control and Prevention, 37.4% of inpatient procedures were performed in patients older than 65 yr in 2010.<sup>2</sup> However, it also indicates that almost two thirds of these procedures were performed in patients younger than 65 yr. The rates of diagnosed diabetes in the civilian population in 2010 were 1.7% between 0 and 44 yr and 12.2% between 45 and 64 yr.<sup>3</sup> These numbers highlight that the pupillary dilatation reflex amplitude evoked by a standardized noxious test to predict movement response to surgical stimulation and individualized administration of general anesthesia could be used in a significant proportion of inpatient procedures.

Studies reporting pupillary autonomic dysfunction in elderly or diabetic patients have examined the changes in pupillary diameter elicited by light/darkness or by mydriatic/myotic eye drops.<sup>4,5</sup> The effects of these two conditions on the changes in pupillary diameter elicited by noxious stimuli such as an electrical current have not yet been examined. The nature and characteristics of the stimuli used affect the amplitude of the pupillary response, and further investigations should examine the consequences of pupillary autonomic dysfunction on the pupillary dilatation reflex to pain in these populations.<sup>6</sup>

Contrary to volatile agents and the minimum alveolar concentration, there is currently no available tool in the United States to predict the absence of response to noxious stimuli when using total intravenous anesthesia. Target-controlled infusions of hypnotic and opioid allowing real-time calculation of effect-site concentrations of both agents are available in Europe but not yet in the United States.<sup>7</sup> This underscores the urgent need for further research in this area

to help anesthesiologists in the administration of total intravenous anesthesia.

As indicated by Larson and Gupta<sup>8</sup> in the accompanying editorial, our study should be viewed as a first step toward “real-time individualized intravenous anesthetics,” and “additional studies examining this pupillary test to predict nonmovement in a more diverse population” are warranted.

### Competing Interests

The authors declare no competing interests.

**Jean Guglielminotti, M.D., Ph.D., Dan Longrois, M.D., Ph.D.** Assistance Publique - Hôpitaux de Paris, Hôpital Bichat-Claude Bernard, Paris Cedex, France (J.G.). jean.guglielminotti@bch.aphp.fr

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## Trials and Observations: A Friendly Pointer on the Language of Study Design

### To the Editor:

I appreciate the fine efforts of Silbert *et al.*<sup>1</sup> to improve our knowledge about patients at risk for postoperative cognitive dysfunction. However, the language used to describe their investigation would benefit from additional precision to improve interpretation and uptake of the study by the readership. Following are a few friendly clarifications.

This letter was sent to the author of the referenced article, who declined to reply.