## Competing Interests

The authors declare no competing interests.

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# Burst-suppression and Postoperative Delirium: Comment

## To the Editor:

The recent report by Pedemonte *et al.*[1] of their substudy of the Minimizing ICU Neurologic Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study[2] emphasized the relationship between electroencephalogram (EEG) burst-suppression during cardiopulmonary bypass and delirium in elderly patients undergoing cardiac surgery. It raises several important points regarding the potential for cerebral monitoring to identify patients who may be at risk for significant postoperative neurologic complications, including delirium and postoperative cognitive dysfunction. However, interpreting these complex relationships requires certain safeguards to minimize the risk of potential false discovery, and thus maximize the confidence in a study's conclusions. These safeguards include, but are not limited to, clear adherence to the prespecified substudy aims and *a priori* hypotheses, the development of a data statistical analytic plan before accessing the data, and consideration to the potential moderating effects in the substudy from the intervention of the parent trial. In this case, for example, the data from the substudy were derived from an ongoing randomized controlled trial investigating the potential effects of dexmedetomidine on postoperative delirium. It would seem reasonable then for any analysis in the substudy to be adjusted for the use of dexmedetomidine. Clarification as to whether and how this was done would be useful.

Several other aspects of their study might also benefit from additional clarity. For example, adherence of reporting to the ordered prestated hypotheses seems to have been modified. For example, the primary hypothesis stated in their introduction was that "preexisting cognitive impairment accounts for electroencephalogram burst-suppression during CPB."[1] It is curious, then, that the article's title, and the subsequent analysis and reporting of the study, principally focuses on postoperative delirium as opposed to preexisting cognitive impairment. This is particularly notable because their power analysis states that the "primary objective of the study was to detect the difference in mean preoperative cognitive scores between the burst-suppression and no burst-suppression groups."[1] The current delirium analysis, as they state, was likely underpowered.

Although there is a potentially important relationship between preexisting cognitive impairment and delirium, and one that could be plausibly mediated *via* EEG burst-suppression, the primary analysis reported should have been the relationship between baseline cognition and EEG burst suppression, with the delirium-related analyses being secondary, and/or exploratory, and fully adjusted for multiple comparisons. Indeed, although some mention is made of adjustments to reduce false discovery, it is not clear where and how these were done. Furthermore, as the authors stated that the "data and statistical analyses plans were defined and written after the data were accessed,"[1] it is not clear how much data and analyses mining might have been undertaken before these complex analyses were settled on and which results were chosen to be reported. The study's actual primary objective found that the relationship between preexisting cognition (assessed using the abbreviated Montreal cognitive assessment) and EEG burst-suppression was not statistically significant ($P = 0.965$ in their table 1).

These limitations should not dissuade the reader from considering the potentially important relationships that the authors have described, because they may in fact be quite meaningful. However, without adequate adjustment for the unit of randomization, consideration for the analytical plan being developed after the data was accessed, and the subsequent organization of the results around a hypothesis that was not the primary one, it does raise the question as to whether undue emphasis is being placed on the "positive"

results surrounding delirium, as opposed to the "negative" results related to baseline cognition.

## Competing Interests

The author declares no competing interests.

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# Burst-suppression and Postoperative Delirium: Reply

## In Reply:

We thank Dr. Grocott[1] for his interest in our article.[2] We share his stated commitment to the core tenets of clear and transparent reporting that support scientific reproducibility. In pursuit of this commitment, we preregistered (NCT02856594) and published the parent clinical trial protocol, including key elements of the statistical analysis plan,[3] and clearly communicated the context of the analyses underlying our retrospective cohort substudy.[2]

Dr. Grocott's concerns primarily relate to our stated hypotheses and the accompanying inferential framework, finalizing our inferential framework after data access, and the positive results we emphasized. We contend that Dr. Grocott's letter raises some of the challenges inherent to the closed peer review process and the need for continued education on the nuances innate to interpreting multivariable regression models. At initial submission, we hypothesized an association between cognitive impairment and burst-suppression during cardiopulmonary bypass. For our inferential framework, we constructed a covariate-adjusted logistic regression model. During the peer review process, it was rightfully suggested that an analysis of postoperative delirium was of interest to our specialty despite the double-blinded ongoing parent trial. Therefore, in our revised submission, we stated an additional hypothesis, "electroencephalogram burst-suppression during cardiopulmonary bypass mediates the effect of cognitive impairment on delirium." Restating our initial hypothesis or increasing our sample size, at this stage, ran counter to our commitment to clear and transparent reporting (please see the Limitations section of our Discussion for the explicit acknowledgment that we powered our study to analyze the association between abbreviated Montreal Cognitive Assessment scores and burst suppression during cardiopulmonary bypass). Thus, our final analysis method was refined after the initial data were accessed to accommodate additional inferences on delirium. Indeed, we intended to convey this by the provided statement concerning the development of the statistical analyses after accessing the data. We acknowledge that it would have been even more precise to have stated that the analyses were modified during peer review.

It is important to note that we did not refer to any of our hypotheses as "the" hypothesis. This is because electroencephalogram hypotheses emanating from the parent trial are exploratory, as stated in our trial protocol.[3] We addressed both our hypotheses using a structural equation model framework, which implied two estimation stages. Thus, we did not deviate from the inferential framework we used at initial submission. Specifically, we estimated the association between burst-suppression during cardiopulmonary bypass and numerous variables in a multivariable model, including the abbreviated Montreal Cognitive Assessment, our cognitive variable of interest. This regression model should be interpreted as follows: adjusting for covariates of interest, the study authors asked whether cognitive impairment was associated with intraoperative electroencephalogram burst-suppression during cardiopulmonary bypass. The final model result, which addressed this hypothesis, is appropriately summarized in the causal diagram we presented in figure 3 (please see supplemental table 7 for univariate results).[2]

In the second stage of estimation, we examined the association between delirium and the same variables in the first stage with the addition of burst suppression. This

regression model should be interpreted as follows: adjusting for covariates of interest, the study authors asked whether burst suppression was associated with delirium. We reported point estimates and 95% CI for this association, and others, to allow readers to evaluate our effect sizes and their plausible values. Thus, we fittingly minimized the sole use of *P* values for inferences as we fully understand that the use of null hypothesis testing can be challenging in analyses with nontrivial model uncertainties. Draper[4] provides additional background that helps with interpreting and assessing model uncertainties. Nevertheless, we reported False Discovery Rate *P* values to help the reader interpret hypothesis tests where appropriate (*i.e.*, univariate regression) throughout the article.

We acknowledge that most studies are rarely definitive. As such, and as stated in our Discussion,[2] our study would benefit from replication studies, including those that adjust for covariates such as dexmedetomidine or multicomponent delirium prevention interventions. However, we believe that the burst-suppression findings and the potentially modifiable physical function findings we reported deserved due emphasis because they are biologically plausible and have clinical implications.

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## Competing Interests

Dr. Akeju has received speaker's honoraria from Masimo Corporation (Irvine, California) and is listed as an inventor on pending patents on electroencephalography monitoring and sleep that are assigned to Massachusetts General Hospital (Boston, Massachusetts). Dr. Houle reports financial relationships with GlaxoSmithKline (Brentford, London, United Kingdom), Eli Lilly (Indianapolis, Indiana), and StatReviewer (North Andover, Massachusetts). The remaining authors declare no competing interests.

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# Balanced Crystalloid *versus* 0.9% Sodium Chloride: What We Overlook in Our Research

## To the Editor:

Infusions of crystalloid solutions are currently recommended for the treatment of critically ill patients with various pathologic conditions, including bleeding, sepsis, and trauma.[1–3] A large number of prospective randomized multicenter studies on the comparative analysis of 0.9% sodium chloride and balanced crystalloid have examined their efficacy and safety. However, the answer to the question of whether the crystalloid composition affects the treatment outcome in critically ill patients has not yet been received.[1] It should be noted that currently, when assessing the pharmacodynamic effects of crystalloid solutions, their actual physicochemical parameters, such as osmolality and pH, are not taken into account. Researchers prefer to use theoretically calculated parameters, and in our opinion, this reduces the accuracy of the results. The fact is that the theoretical osmolarity values of solutions can differ significantly from their actual osmolality values. We suggested that the same crystalloid solutions provided by different manufacturers may have different values of both osmolality and pH. To prove that, we studied physicochemical parameters (osmolality