

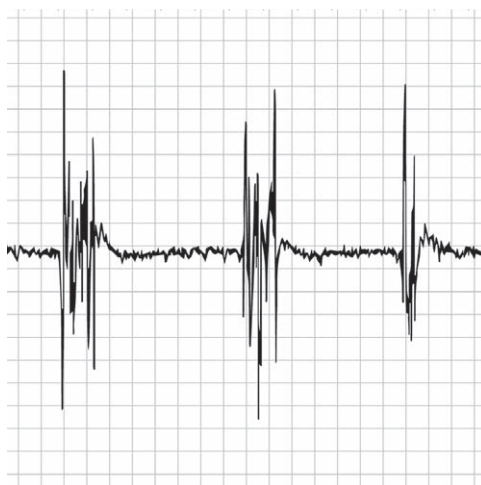
# Postoperative Delirium

## A Minefield of Markers and Mediators

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The burst suppression pattern in the electroencephalogram (EEG) is not seen in healthy physiology. Therefore, it is a seductive idea that the appearance of this pattern is an indicator of brain pathology and that elderly patients showing intraoperative burst suppression may then go on to develop disrupted cognitive function postoperatively. In this issue of the journal, a study by Pedemonte *et al.*<sup>1</sup> replicates the results from a number of previous observational studies, showing that intraoperative burst suppression was associated with a marked increase (from 6 to 25%) in postoperative delirium after cardiac surgery. From table 1 of their article, 15 of the 20 patients who had postoperative delirium had displayed a burst suppression EEG pattern during their surgery.

Pedemonte *et al.* found that the lowest intraoperative temperature, EEG  $\alpha$  power, and physical function were associated with the development of burst suppression while on cardiopulmonary bypass. In addition, age and burst suppression were associated with postoperative delirium. These observations are entirely consistent with a previous larger study looking at the role of intraoperative EEG in postanesthesia care unit delirium.<sup>2</sup> However, the “novelty” in their article is that they then attempted to dissect out the exact role of intraoperative burst suppression from within all these other possible causes of postoperative delirium. To illustrate their process of analysis, the authors made causal diagrams—figures 1 and 3 of their article. However, the low patient numbers and limited data collection precluded a full causal analysis to exclude mediator-outcome confounding variables. The inclusion of burst suppression in the multivariable model effectively wiped out (or blocked) the associations of the other upstream factors



**“...burst suppression is better described as a ‘marker’ of an abnormal brain response to anesthesia and surgery—not a causal mediator.”**

with postoperative delirium. They concluded that burst suppression is lying causally downstream of the other factors and therefore “mediates” these effects. It is tempting to assume that the article implies that altering anesthesia delivery to reduce the burst-suppression pattern should, in turn, reduce postoperative delirium. Although there is ongoing debate about this,<sup>3,4</sup> any beneficial therapeutic effects are probably quite modest. The Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) randomized controlled trial suggested that modification of volatile concentration to reduce burst suppression using current EEG practices did *not* reduce postoperative delirium in noncardiac surgical patients. A recently published article by Fritz *et al.*<sup>5</sup> reported a mediation analysis done on a subset from this trial. In contrast to the results of Pedemonte *et al.*,<sup>1</sup> Fritz *et al.*<sup>5</sup> found that burst suppression mediated only a small amount of the delirium.

To make sense of these contradictory conclusions, we need to ask the question: “What exactly is a mediator?” Unfortunately, there are several different answers to that simple question. A formal statistical definition—as used in this article—is that a mediator is a variable that lies between two other variables and that influences the relationship between them. However, a more commonsense definition is that a mediator is part of (or tightly linked to) the *mechanism* by which an exposure causes its effects. If we say that burst suppression (an EEG pattern) mediates the effects of the other factors on postoperative delirium, we are saying that these other factors would *not* be able to cause (as much) delirium, unless they specifically interacted with the anesthesia and surgery in such a way as to produce a

Image: J. P. Rathmell.

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pathologic intraoperative brain state that was manifest as a burst suppression pattern in the EEG.

To help us appreciate the different mediator definitions, we can look to analogies from cardiology. With appropriate caveats for false positives and false negatives, we can say—in the formal statistical sense—that both ST elevation and appearance of ventricular ectopy “mediate” the development of myocardial ischemia from preexisting coronary vascular disease. Both are associated with episodes of myocardial ischemia. However, the efficacy of interventional treatments to reverse ST elevation (e.g., coronary revascularization,  $\beta$  blockers) shows that ST elevation is tightly linked to the true causal mechanistic mediator, which is a coronary thrombus of sufficient size to cause myocardial ischemia. Conversely, the effective treatment of ventricular ectopics with iv lidocaine is not treating the mechanistic cause of the ischemia at all and had negligible effect on the outcome in most cases. Although ventricular ectopy might formally be a statistical mediator, it is not even close to being a causal mediator of myocardial ischemia. It is a *marker*. We would suggest that burst suppression is better described as a “marker” of an abnormal brain response to anesthesia and surgery—not a causal mediator. The actual mediator(s) lie in the details of the pathologic brain response, of which the EEG pattern is only a flag. Counterfactual examples abound. Burst suppression can be induced in young subjects without cognitive impairment,<sup>6</sup> and patients having awake spinal anesthesia can get postoperative delirium. To make progress with these questions, future work needs to use a combination of advanced statistical techniques to quantify the relative contributions of all important causal factors (including biologic markers of inflammation) and the interactions between them.

The most robust conclusion of the study is that a number of intraoperative EEG patterns (low midfrequency/ $\alpha$  power and/or increased burst suppression) are important, easily obtained markers of physiologic “functional brain fragility/age” that serve to warn of a high likelihood of postoperative problems—and allow appropriate individualized patient care plans to be instituted to minimize delirium. These might include drug treatments (such as giving dexmedetomidine or haloperidol and avoiding anticholinergic drugs, opioids, and midazolam) and disposition of the patient to wards with appropriate levels of nursing care.

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## References

1. Pedemonte JC, Plummer GS, Chamadia S, Locascio JJ, Hahn E, Ethridge B, Gitlin J, Ibalá R, Mekonnen J, Colon KM, Westover MB, D'Alessandro DA, Tolis G, Houle T, Shelton KT, Qu J, Akeju O: Electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients mediates postoperative delirium. *ANESTHESIOLOGY* 2020; 133:280–92
2. Hesse S, Kreuzer M, Hight D, Gaskell A, Devari P, Singh D, Taylor NB, Whalin MK, Lee S, Sleight JW, García PS: Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanesthesia care unit: An early sign of postoperative complications. *Br J Anaesth* 2019; 122:622–34
3. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group: BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013; 25:33–42
4. Punjasawadwong Y, Chau-In W, Laopaiboon M, Punjasawadwong S, Pin-On P: Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. *Cochrane Database Syst Rev* 2018; 5:CD011283
5. Fritz BA, King CR, Ben Abdallah A, Lin N, Mickle AM, Budelier TP, Oberhaus J, Park D, Maybrier HR, Wildes TS, Avidan MS, Apakama G, Aranake-Chrisinger A, Bolzenius J, Burton J, Cui V, Emmert DA, Goswami S, Graetz TJ, Gupta S, Jordan K, Kronzer A, McKinnon SL, Muench MR, Murphy MR, Palanca BJ, Patel A, Spencer JW, Stevens TW, Strutz P, Tedeschi CM, Torres BA, Trammel ER, Upadhyayula RT, Winter AC, Jacobsohn E, Fong T, Gallagher J, Inouye SK, Schmitt EM, Somerville E, Stark S, Lenze EJ, Melby SJ, Tappenden J, ENGAGES Research Group: Preoperative cognitive abnormality, intraoperative electroencephalogram suppression, and postoperative delirium: A mediation analysis. *ANESTHESIOLOGY* 2020; 132:1458–68
6. Shortall BP, Hickman LB, Mak-McCully RA, Wang W, Brennan C, Ung H, Litt B, Tarnal V, Janke E, Picton P, Blain-Moraes S, Maybrier HR, Muench MR, Lin

N, Avidan MS, Mashour GA, McKinstry-Wu AR, Kelz MB, Palanca BJ, Proekt A; ReCCognition Study Group: Duration of EEG suppression does not predict

recovery time or degree of cognitive impairment after general anaesthesia in human volunteers. *Br J Anaesth* 2019; 123:206–18