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Postoperative delirium and postoperative cognitive dysfunction: Two sides of the same coin?

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Are postoperative delirium and postoperative cognitive dysfunction (POCD) entirely separate disorders, or are they two manifestations of the same underlying spectrum of postoperative neurocognitive dysfunction? Evidence exists in support of both the “splitters” (who view these as two completely different disorders) and the “lumpers” (who view these disorders as two parts of the same spectrum of postoperative neurocognitive dysfunction; Fig 1). Indeed, this nosological debate is not unique to anesthesiology; nosological debates have been at the heart of classifying medical disorders and syndromes ever since Victor McKusick used and illustrated the terms “splitters” and “lumpers” in 1967.¹ In this issue of Anesthesiology, Brown and colleagues provide further evidence in favor of the “lumpers” position, by demonstrating that delirium after cardiac surgery is associated with worse cognitive function at 1 month after surgery.² Before further discussion of these findings, it is worth reviewing the evidence on each side of the “splitters” vs “lumpers” debate about postoperative delirium and POCD.

The splitters can point to at least four key differences between postoperative delirium and POCD. First, these syndromes are measured in different ways. Postoperative delirium is typically assessed by instruments that evaluate attention, level of consciousness and disorganized thinking, such as the CAM-ICU or 3D-CAM.³ In contrast, POCD is typically assessed by a drop in cognitive performance from before to after anesthesia and surgery on detailed neuropsychological testing.⁴ Second, these syndromes don’t necessarily include deficits in the same cognitive domains. All patients with delirium have attention deficits, while many patients with POCD show deficits in other cognitive domains (such as memory or executive function) and do not have attention deficits. Third, these syndromes occur at different times. Postoperative delirium is typically assessed within days after surgery and shows a peak incidence on postoperative days 1–3 while POCD is typically assessed at 1–3 months after surgery. Fourth, there are few if any human studies demonstrating that these disorders share the same pathophysiologic mechanisms.

On the other side of this debate, the “lumpers” can point to at least four key similarities between postoperative delirium and POCD. First, several risk factors are common to both

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postoperative delirium and POCD, such as lower preoperative education level, poor preoperative cognitive function, and depression.⁵ Second, postoperative delirium and POCD (occurring between 6–12 weeks after surgery) are both associated with worse cognitive decline in the 3–5 years after anesthesia and surgery,^{4,6,7} decreased quality of life,⁸ and increased 1 year postoperative mortality risk.⁹ Third, animal studies raise the possibility that common pathophysiologic processes such as neuro-inflammation and Alzheimer's disease pathology may play a role in both postoperative delirium and POCD.⁵ Fourth, many patients with delirium develop postoperative cognitive deficits, and conversely, many patients with POCD also had postoperative delirium earlier in their postoperative recovery period (reviewed in Berger *et al*⁶).

This last point is further strengthened by the findings of Brown and colleagues in this issue of *Anesthesiology*.² They show that in a cohort of 142 cardiac surgery patients, patients with postoperative delirium had significantly worse cognitive function at 1 month after surgery. It is unclear how much of this cognitive decline was really associated with delirium versus lower baseline cognitive function, since the results were not adjusted for baseline cognition. This is a key issue, since it raises the question of whether delirium is simply a marker for other factors that may contribute to POCD risk, such as lower preoperative cognitive status, versus whether delirium itself actually contributes to longer term POCD. Nonetheless, the Brown *et al* study² corroborates prior work by Sacyzynski *et al*⁷ and Inouye *et al*,⁶ both of whose studies did adjust for baseline cognitive status and demonstrated that patients with postoperative delirium had worse postoperative cognitive trajectories than patients who didn't develop postoperative delirium. Interestingly, Brown and colleagues found no difference in 1-year postoperative cognitive function when comparing patients who did (versus those who did not) develop postoperative delirium, while other studies have found that patients with postoperative delirium do have worse 1 year postoperative cognitive function than patients who did not develop postoperative delirium.^{6,7} The discrepancy between these findings may reflect the use of different cognitive assessment tools, differing characteristics among these different study cohorts, or simply insufficient power in the Brown *et al* study (a type II statistical error). This last point is a reasonable concern, as the studies that have shown one year postoperative cognitive differences between patients with vs. without delirium had ~2–4-fold larger cohort sizes than the Brown *et al* study.^{6,7} Despite these limitations, the Brown *et al* study demonstrates that patients with postoperative delirium have worsened cognitive function at 1 month after surgery.² Since we have recently argued that POCD should be conceptualized as a syndrome with a continuous severity distribution,⁵ these data suggest a link between delirium and increased POCD severity.

So where do we go from here? The debate about the relationship between postoperative delirium and POCD persists partly because we have an extremely limited pathophysiological understanding of either disorder. In order to understand the extent of similarity between these disorders and why each is associated with long-term cognitive decline, we need to understand at least three things. First, we need a full understanding of what delirium and POCD are at a biological level, ranging from the levels of molecules, to cells, to brain circuits and activity patterns and ultimately to the dysfunctional neurocognitive processes of each disorder. Second, we need to understand the perioperative factors that contribute to

alterations at each of these levels. Third, we need to understand the longer-term trajectory and implications of such pathophysiologic alterations.

Elucidating these pathophysiological mechanisms of postoperative delirium and cognitive dysfunction is a non-trivial research endeavor that will likely occupy investigators for decades. Yet, there are relatively simple places to start. One potential opportunity is to take a closer look at medical disorders such as obstructive sleep apnea (OSA) that predispose patients to postoperative delirium and cognitive decline and study what specifically predisposes these patients to these disorders. For example, patients with OSA have increased levels of systemic inflammatory cytokines, morphologic brain changes, and higher rates of long-term cognitive decline compared to non-OSA patients.¹⁰ Studying specific neuro-inflammatory processes in OSA patients (vs. non-OSA patients) before and after surgery, and assessing these patients for delirium and POCD, provides an opportunity to investigate pathophysiologic processes that may play an etiologic role in these disorders. Further, such studies could help lead to future treatments for delirium, POCD and even comorbid disorders such as OSA. And, since anesthesiologists are both airway experts and perioperative physicians, who else is better positioned to understand the links between a disorder that involves the airway (OSA) and common perioperative complications such as delirium and POCD?

Regardless of whether OSA or any other specific comorbid illness contributes to postoperative delirium and cognitive dysfunction risk, the findings of Brown *et al.* and other studies indicate that postoperative delirium is associated with longer-term postoperative cognitive dysfunction. The key questions for the field now are to understand the mechanism(s) of this association, and to clarify the extent to which preventing postoperative delirium also reduces longer term POCD.

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Figure 1.

The Lumpers and the Splitters*

*Any resemblance in these figures¹ to any historical figure or any political, social or other judgement is unintended on our part.

McKusick, Victor A. "On Lumpers and Splitters, or the Nosology of Genetic Disease." *Perspectives in Biology and Medicine* 12:2 (1969), Fig. 1. © Johns Hopkins University Press. Reprinted with permission of Johns Hopkins University Press.