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Opinion

Anesthesia and Postoperative Cognitive Dysfunction

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Many of us may have a friend or family member who underwent surgery and perhaps did not quite seem like him- or herself afterwards. This affect change may have quickly resolved, or it may have lingered for quite some time. While stories like this may indeed be anecdotal, the notion that surgery and anesthesia may contribute to cognitive dysfunction has been around for years. In fact, this phenomenon was described by Henry Jacob Bigelow in 1846 shortly after the infamous public demonstration of ether anesthesia by William T.G. Morton (1). In the article "Insensibility during Surgical Operations Produced by Inhalation", Bigelow remarks, "The character of the lethargic state, which follows this inhalation, is peculiar."(1). He also subsequently describes a patient in which the "narcotism was complete during more than twenty minutes, the insensibility approached to coma." (1). Many years later, in 1961, Eckenhoff et al. wrote about the phenomenon of "postanesthetic excitement" and retrospectively surveyed patient charts for associated risk factors (2). Documentation of post operative alteration in cognition has persisted, and more recently concern has grown that these alterations may in fact last beyond the perioperative setting. Newer data demonstrate that postoperative cognition dysfunction (POCD) may in fact cause long-term harm to patients (3, 4).

POCD is loosely defined, though characterization involves the decline of various neuropsychological domains such as memory, speed of processing, and executive functioning (5). Specific scientific inquiry has focused on the elderly, where POCD is more common (4, 5). Emerging basic science research has shown that anesthetics themselves may contribute to cognitive impairment in aged animals (6). This notion is based on lab work demonstrating neurotoxic effects of anesthetics in vitro and in vivo, including caspase activation, apoptosis, accumulation and oligomerization of beta-amyloid protein, and neuroinflammation (7-9). With an aging population and a growing surgical volume in the United States (10), anesthetic exposure to patients may also continue to grow in volume. If surgery and anesthesia do contribute to POCD, this could represent a large socioeconomic and psychological burden on the population over the coming years. As outlined in this commentary, paramount goals in the field of perioperative medicine should be to (1) discover the extent to which surgical and anesthetic factors contribute to POCD in the clinical setting, and (2) develop systematic, concerted efforts to address and reduce the effects of any perioperative factors that may exacerbate POCD.

Anesthesia and POCD

With regards to anesthesia in particular, both anesthetic technique (i.e. regional vs. general anesthesia) and types of anesthetics within groups (i.e. comparisons among various volatile anesthetics) have been compared with regards to subsequent rates of POCD. A recent meta-analysis demonstrated no correlation between anesthetic technique and post operative delirium (POD), though it did show a non-statistically significant increase in POCD incidence with general anesthesia as compared to various regional anesthesia techniques (11). Multiple confounders surface, however, when trying to prospectively study POCD in this manner. The studies in this analysis all varied in terms of sample size, cognitive testing approach, follow- up times, and even the way in which POCD was defined. A standardized, accepted definition of POCD may serve as a foundation upon which subsequent clinical studies can be based. From here, further heterogeneity in study variables may become reduced. As men-

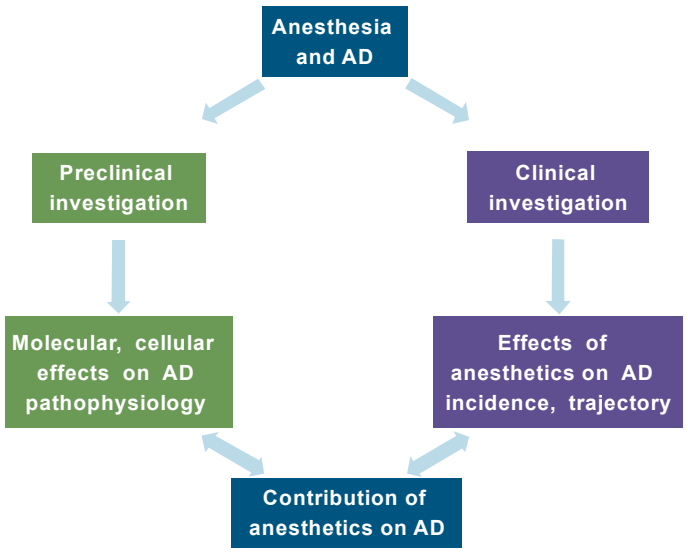

Figure. Proposed Research Paradigm for Future Research Involving Anesthesia and Alzheimer's Disease (AD).
To further delineate the exact contributions of anesthesia on AD (if any), interplay between laboratory and clinical research may be needed.

tioned above, POCD incidence has also been compared in groups exposed to different intravenous and inhalational anesthetic agents. Unfortunately, many of the studies conducted have not been adequately powered statistically to detect consistent differences in cognitive trajectory or follow cognitive changes long- term. Small, prospective trials have demonstrated that desflurane may be associated with faster recovery profiles compared to other anesthetic agents (12), with one pilot study even demonstrating a lower incidence of POCD compared to isoflurane anesthesia (13). Again, however, we must stress that larger, more adequately powered studies are required to draw stronger conclusions with regards to respective anesthetic agents' effects on postoperative cognitive function.

Anesthesia and Alzheimer's Disease

Anesthetics may also play a role in the developing pathophysiology of neurodegenerative disorders such as Alzheimer's disease (AD). Various preclinical studies have demonstrated that the volatile agent isoflurane, for example, propagates AD pathophysiology at various cellular and molecular levels (7- 9). This has been demonstrated as well to some extent for both sevoflurane (14) and propofol (15), with both beta- amyloid protein processing and tau hyperphosphorylation being the proposed mechanisms by which these anesthetics may contribute to AD pathology (16). At this point, much of the data remain in the preclinical stage, though clinical studies are forthcoming. In fact, recent clinical studies evaluating cerebrospinal fluid (CSF) concentration of beta-amyloid and tau protein levels have implicated these proteins in the development of postoperative cognitive changes, which desflurane showing a potentially favorable profile (17). In addition, other studies have investigated the potential association between anesthesia, CSF biomarkers, POCD and postoperative delirium (18, 19). Again, however, cognitive testing in AD patients as a function of anesthetic exposure remains on the horizon. Likely, a translational research strategy including both preclinical and clinical investigation may be necessary to draw further, solidified conclusions with regards to anesthetics and AD (Figure).

Future Directions

At present, the anesthesiologist is in a great position to lead the charge with regards to advances in perioperative neuroscience. On a daily basis, anesthesiologists induce a reversible comatose- like state in patients prior to their surgery (20), evaluate the brain activity in the operation room via potential electroencephalogram (EEG) monitoring, and safely facilitate the emergence from anesthesia. This platform of applied clinical neuroscience serves as a great foundation from which to launch exploratory efforts into the realms of consciousness and cognition. With further inquiry, we may be able to develop strategies for preventing, temporizing, and treating POCD. Through this work, we may also gain a better understanding of the biologic substrates of consciousness and cognition as well. Ultimately, we may then become able to better

characterize and manage the different shades of consciousness Henry Jacob Bigelow described under ether anesthesia over 150 years ago.

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