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The Role of the Aging Brain-Heart-Immune Axis in Postoperative Delirium

Abstract

Postoperative delirium (**POD**) is a syndrome of acute fluctuating changes in attention and consciousness that affects up to 50% of surgery patients 65 and older, increases the risk for Alzheimer's disease (AD) and AD-related dementias (ADRD), and accelerates dementia progression. Yet, interventions for POD are limited because its pathophysiologic mechanisms are poorly understood.

The vagus nerve mediates the brain-heart-immune axis, which allows the brain to suppress systemic inflammation via the cholinergic anti-inflammatory reflex. Advanced age, preoperative stressors, the condition requiring surgery, and surgery and anesthesia themselves all decrease vagal tone. Without sufficient vagal tone to keep inflammation in check, excessive inflammation will result, including neuroinflammation. Excessive postoperative inflammation is thought to play a role in POD pathogenesis. Furthermore, excessive postoperative inflammation can injure neurons, providing a plausible mechanistic link between POD and AD+ADRD. Thus, there is a critical need to evaluate the role of the brain-heart-immune axis in POD among older adults.

To interrogate the aging brain-heart-immune axis as a possible contributor to POD pathogenesis, heart rate variability (HRV), the standard measure of vagal tone, will be measured before general surgery in 100 patients 65 and older. *Specifically*, the prospective, observational **HIPPIE** – **H**RV **I**n **P**OD and **P**ostoperative **I**nflammatory **E**ndpoints - study will quantify the relationship between preoperative vagal tone and **(1)** POD incidence and **(2)** postoperative increase in serum biomarkers of inflammation and neuronal injury. Successful completion of the HIPPIE study will demonstrate the involvement of the brain-heart-immune axis in POD pathogenesis and will provide novel biomarker(s) of POD risk. Furthermore, a mechanistic link between POD and the brain-heart-immune axis is anticipated to provide strong scientific justification for future trials of vagal tone enhancement as an intervention for POD. Finally, this work will provide a rich new perioperative geriatric data set including measurements of the previously unexplored perioperative brain-heart-immune axis. The data, experience, and training from this proposal will lay the foundation of a successful career in geriatrics research