Title: Uncovering mechanisms of brain dysfunction across the continuum of critical illness

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Structured Abstract:

Background: Cognitive impairment is a common problem in ICU patients. While prior studies identified demographic and clinical risk factors, the underlying biologic mechanisms remain largely unexplored. Given high prevalence of ischemic lesions in ICU patients, we explored ischemia as a potential mechanism for ICU-related cognitive impairment across the continuum of critical illness by establishing whether: 1) certain patient groups are more vulnerable to ischemia prior to onset of critical illness, 2) spontaneous variations in cerebral blood flow velocity (CBFv) during critical illness can accumulate over time and represent a plausible ischaemic insult, and 3) web-based cognitive battery can be used to measure cognitive outcomes following resolution of critical illness.

Methods: We used transcranial Doppler to measured cerebrovascular reactivity (CVR) to CO2 as a marker of cerebrovascular function in hemodialysis (HD) and chronic kidney disease (CKD) patients, as well healthy controls. In the second study, we used transcranial Doppler to monitor CBFv for up to 8 hours in critically ill patients presenting with respiratory failure and shock. We then computed the incidence and duration that CBFv deviated from baseline beyond ischemic thresholds and determined whether these deviations are associated with impaired cerebral autoregulation. In the last study, we assessed the feasibility of using web-based cognitive battery to measure cognitive outcomes in ICU survivors as a means to assess consequence of ischemic injury.

Results: Compared to CKD patients and healthy controls, HD patients have impaired cerebrovascular reserve as indicated by lower CVR. We then showed that in critically ill patients with respiratory failure and shock, CBFv deviates from baseline beyond ischemic thresholds 12-20% of observation time, and that these deviations are associated with impaired autoregulation. In our last study, we demonstrated that a web-based cognitive battery is feasible for detecting multidomain cognitive impairment in ICU survivors. We identified battery duration as a feasibility constraint that we successfully addressed by shortening battery length from 12 to 6 tests while preserving its diagnostic utility.

Conclusion: Given that HD patients are at higher risk of ICU admission, impaired CVR represents the first functional risk factor for ischemic brain injury that may predispose these patients to ICU-related cognitive impairment. During critical illness, observed deviations in CBFv are a plausible insult that can lead to ischemic injury, especially in the observed settings of impaired cerebral autoregulation. Web-based cognitive battery provides a feasible means to identify and track consequences of ischemic injury in ICU survivors. Future studies should establish whether impaired CVR and deviations in CBFv beyond ischemic thresholds are associated with higher burden of imaging markers of ischemia and cognitive impairment.