

Ventilator-Associated Brain Injury - A Priority for Research in Mechanical Ventilation



Mechanical ventilation can lead to complications like ventilator-induced lung injury and ventilator-induced diaphragm dysfunction. However, there may be other forms of ventilator-associated issues that require understanding to improve outcomes for patients on mechanical ventilation. In particular, ventilator-associated brain injury (VABI) should be given priority to determine if implementing brain-protective ventilation strategies could improve outcomes for critically ill patients.

Mechanical ventilation can exacerbate existing brain injuries like stroke or traumatic brain injury. However, recent evidence indicates that ventilation itself can cause brain injury in patients without prior brain issues. - i.e. VABI. VABI is defined as a new brain injury or dysfunction directly caused by mechanical ventilation, excluding other factors like sedation or concurrent interventions.

Pre-clinical research indicates that positive pressure ventilation alone can trigger acute inflammation and cellular apoptosis in various brain regions. In animal models without pre-existing brain injury, positive pressure ventilation disrupted blood-brain barrier function, leading to neuroinflammation and apoptosis in the hippocampus. The observed neuropathology resembles that seen in Alzheimer's disease.

In murine and porcine models, VABI is directly related to the intensity and duration of mechanical lung stress and strain from positive pressure ventilation. Increased neuronal activity due to this stress activates pathways leading to neuronal injury and acute neuroinflammation. High tidal volumes exacerbate neuronal apoptosis in various brain regions, while very low tidal volumes reduce cerebral pro-inflammatory cytokines compared to standard volumes. Higher driving pressure and mechanical power also contribute to neuroinflammation and apoptosis. Cognitive impairment resulting from brain injury correlates with the duration of ventilation, as observed in studies where mice ventilated for longer periods exhibited worse cognitive scores persisting even after extubation.

Evidence suggests a correlation between injurious mechanical ventilation and long-term neurological outcomes. In a retrospective study of out-of-hospital cardiac arrest patients, lower tidal volumes (< 8 ml/kg) during the initial 48 hours after hospital admission were linked to better neurological outcomes at discharge. Additionally, a systematic review found a consistent relationship between mechanical ventilation duration and delirium risk, which is itself a significant factor for long-term neurocognitive impairment. This impairment affects up to one-third of patients surviving mechanical ventilation, persisting even a year after their initial illness.

Pre-clinical studies propose various strategies to mitigate VABI. Firstly, limiting lung stress and strain by avoiding high driving pressures during positive pressure ventilation may attenuate VABI. Secondly, pharmacological or neuro-modulatory approaches have been suggested, such as nebulised lidocaine to antagonise pulmonary stretch receptors or intratracheal administration of an experimental drug (iso-PPADS-tetrasodium) to block pulmonary purinergic receptors. Additionally, techniques like olfactory bulb stimulation or diaphragm neurostimulation could be explored in future randomised trials. Clinical studies have shown that olfactory bulb stimulation activates the default mode network in coma patients, potentially improving cognition. The mechanisms behind these interventions' efficacy in preventing VABI remain unclear, but they suggest that spontaneous breathing or olfactory bulb stimulation during assisted ventilation might offer protection against VABI.

The concept of VABI is currently a hypothesis with uncertain clinical significance, and the precise mechanisms linking positive pressure ventilation to brain injury require further elucidation. Defining and validating VABI in clinical settings necessitates assessing the correlation between injurious mechanical ventilation settings and measures of brain inflammation, injury, and dysfunction, particularly within randomised trials of protective ventilation strategies. The confounding effects of co-interventions like sedation need careful investigation. Developing assays such as biomarkers or imaging techniques to detect VABI would greatly facilitate clinical research, with candidate biomarkers including S100 β , glial fibrillary acid protein (GFAP), ubiquitin c-terminal hydrolase L1 (UCHL1), and neurofilament light chain (NfL). Electrophysiological monitoring or functional imaging may also aid in detecting VABI, though their relationship with VABI requires careful examination due to confounding factors. If a working clinical definition of VABI can be validated, its manifestations, associated risk factors, and long-term outcomes can be systematically characterised. Ultimately, strategies to prevent VABI during mechanical ventilation, termed 'brain-protective ventilation', should be developed and

rigorously evaluated.

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