

Editorial

Gravitational ischemia in the brain—may contribute to delirium and mortality in the intensive care unit

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Recently, a group of Critical Care Medicine (CCM) investigators [1] reported on a population-based retrospective cohort study of delirium in hospitalized adults. They were studying the effects of delirium in the intensive care unit (ICU) on post-hospital discharge mortality—and the primary outcome for their study was mortality. Over 10,000 patients were included in the overall study cohort—drawn from 14 hospitals over 2.5 years. The CCM investigators discovered that delirium in the ICU was associated with increased mortality during the first 30 days following hospital discharge. Patients who died during hospitalization did not meet the inclusion criteria for this study, but those patients who died during hospitalization, were over three times more likely to have experienced delirium as those who survived.

But why do patients who experience delirium in the ICU also experience a higher incidence of near-term mortality? Many factors may be involved—medication adverse effects, electrolyte imbalance, occult infection, occult malignancy, and occult coronary disease are only a few. Currently unexplored, however, regarding ICU delirium is the role of gravity in the brain. Encased in the skull, the brain is one of the least mobile and least accessible organs in the body. The external surfaces of the brain lie still against the relatively hard inside surfaces of the skull. The meninges and cerebrospinal fluid surrounding the brain may pro-

vide some cushioning, but do not mitigate the effects of gravity. In contrast, the heart and lungs are continuously in motion—and they are surrounded by soft tissues.

Gravitational ischemia in the brain results from the mass effect of one part of the brain upon another in a gravitational field [2–4]. In any given head position, the “top” half of the brain (farthest from the center of the earth) is sitting on the “bottom” half as a weight-burden. In healthy individuals, head and body positions are roughly vertical for 16 hours a day, and then roughly horizontal for eight hours at night during sleep. Pancaking layers of progressively increasing weight from the over-lying brain tissue compress blood vessels and reduce blood flow in the bottom layers, resulting in regional gravitational ischemia on the bottom side of the brain [2–4]. Ischemia is reversible in its early stages.

In healthy individuals, the horizontal body positioning associated with sleep (often with nose up, and back of the head down) helps to redistribute both gravitational ischemia and blood flow—after a 16-hour period of vertical head positioning during the waking hours of the day. Restoration of blood flow by reopening of capillary vascular beds follows repositioning (unloading of ischemic regions) of the brain relative to gravity—by head tilting, which is significant through the 24-hour sleep/wake cycle [2–4].

But for many ICU patients, the supine position becomes their primary head and body position during what would normally be the waking hours of the day—as well as at night. The down-side occipital (visual) cortex incurs gravitational ischemia—and the neighboring visual association cortex likely becomes ischemic as well. As orientation begins to deteriorate, the precise configuration of visual images may become somewhat distorted—and their meaning and significance may become very distorted. Staff moving around in the ICU may be inter-

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preted as animals, or a room filled with electronic monitors may be interpreted as an airplane cockpit [2–4].

Any injury or metabolic insult to the nervous system, such as ischemia, may simultaneously or alternately produce paired signs or symptoms, one “positive” (displaying aberrant hyperactivity) and the other “negative” (displaying partial inactivity) in terms of the specific function of the involved neural tissue. Common pairs include tingling and numbness, tinnitus (ringing) and hearing loss, manic and depressive thoughts and behavior, scintillating scotomas, and blind spots [2–4].

Consistent with this, some of the CCM investigators [5] had previously reported on the differing clinical patterns of the delirium subtypes: hyperactive and hypoactive. Their finding that hypoactive delirium (as opposed to hyperactive) was more associated with mortality was consistent with hypoactive patients spending more time in a single body position—probably supine—and developing the greatest degree of gravitational ischemia in the brain.

Additionally, the manner in which ICU patients are cared for often promotes gravitational ischemia in the brain. There is decreased physical activity in general, which is associated with fewer changes in head-tilting. More bed rest and sedative medications promote longer continuous periods of time in supine position. And mechanical ventilation may create some huge problems. Supine position is considered

sary to facilitate management of the endotracheal tube and its various connections to the ventilator. Often overlooked in ICU delirium prevention is the arterial partial pressure of carbon dioxide (CO_2), and its effects on brain circulation, where CO_2 is a potent vasodilator globally (throughout the entire brain) [6–10]. Even small increments of reduced pCO_2 lower than 40 mm Hg can cause significant cerebral vasoconstriction. Many normal adults who take five deep breaths quickly will begin to feel light headed.

And mortality is not a new association with gravitational ischemia in the brain. Sudden unexpected death in epilepsy was one of the first diseases implicated [4]. Additionally, the solitary tract nucleus of the medulla with its limited watershed vascular capacity may occasionally be the focus of transient ischemia caused by the increased metabolic demands associated with frequent and intense neuronal stimulation from other organs and other parts of the brain—as would typically occur in an ICU setting. Case reports [11,12] have suggested that these focal ischemic changes may sometimes result in the initiation of intense autonomic discharges, which can occasionally be fatal. On the other hand, detailed postmortem examinations of victims of sudden unexpected death have revealed in some cases no cause of death except for the presence of a brainstem lesion [13,14]. Decreased arterial CO_2 in the brain causes vasoconstriction, which reduces blood flow and worsens ischemia in medullary autonomic nuclei. An abnormal neural dis-

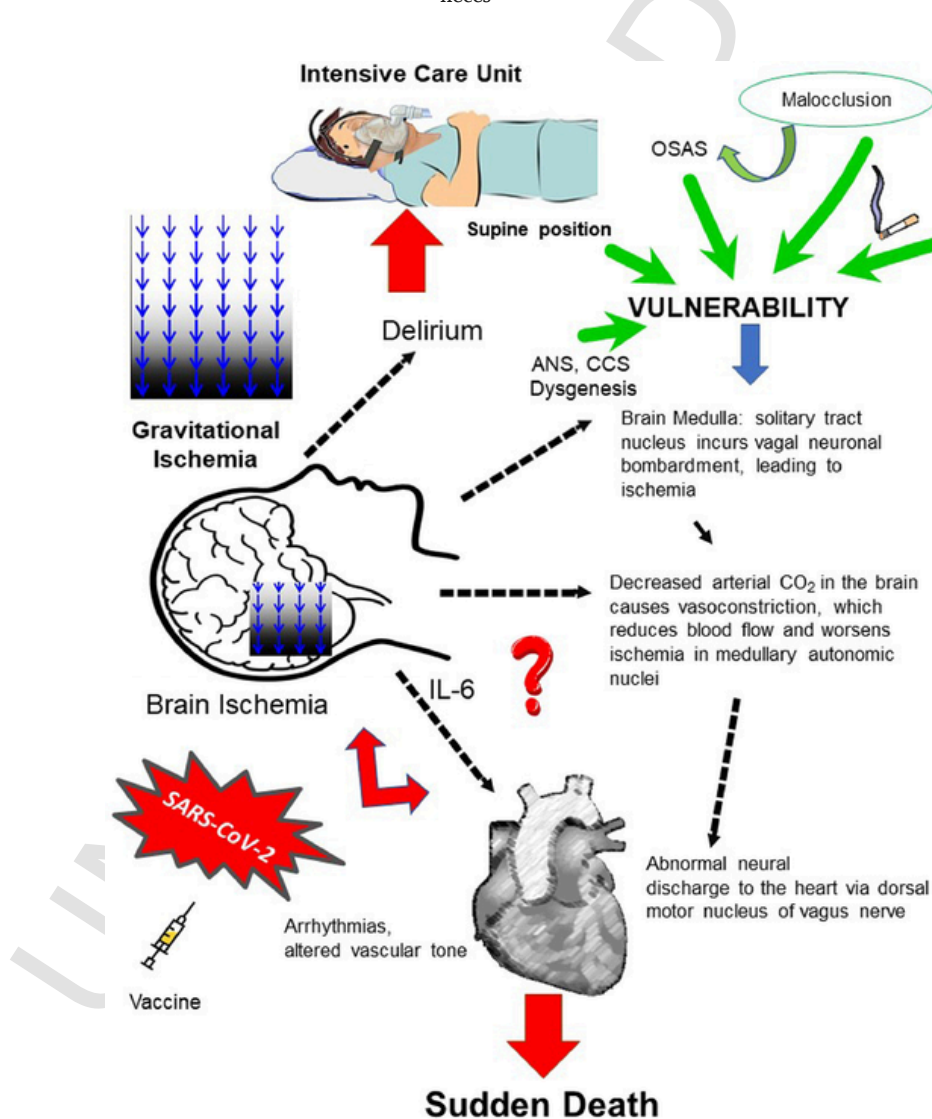


Fig. 1. Diagram of the possible relationship between gravitational ischemia in the brain, incurred during prolonged supine position, in a patient in the intensive care unit, resulting in delirium and sudden death. ANS, autonomic nervous system; CCS, cardiac conduction system; OSAS, obstructive sleep apnea syndrome.

charge to the heart via dorsal motor nucleus of vagus nerve would follow, resulting in arrhythmias, altered vascular tone, and sudden death. Obstructive sleep apnea syndrome (OSAS) is the most common form of sleep-disordered breathing that affects approximately 10% of the adults and 5% of children [15]. Clinically silent mutations of the *PHOX2B* gene can lead to structural and functional modification of their product providing to a group of children with malocclusion similar features to those of sleep apnea episodes and craniofacial malformations [16]. Over the years, outcomes of different therapy modalities for OSAS have been evaluated [17,18], but the common sudden death-OSAS' etiology is largely unknown due to lack of specialized multidisciplinary post-mortem and clinical studies, and due to as yet undetermined environmental co-factors [19]. Recently, studies on patients dying suddenly from COVID-19 identified high levels of IL-6 [20], the same cytokine that has been hypothesized to be elevated in OSAS correlated with sudden unexpected death [19,21] (Fig. 1).

Although much more research is needed in this area, it is interesting to consider that three independent physiological sources of brain ischemia (one focal, one regional, one global) can be easily superimposed upon each other to produce dramatic consequences, and all in the absence of any occlusive cerebrovascular disease, traditionally thought of as the cause of brain ischemia, and which would typically be associated with strokes and transient ischemic attacks. The ICU is one of the most likely settings for this to occur, because it challenges brain physiology in so many different ways. Fortunately, gravitational ischemia in the brain is largely preventable by frequently changing the head tilt—just as ischemic skin breakdown, bed sores, and decubitus ulcers are currently prevented by frequent changes in general body positioning, focused on the effects of gravity. After the patient succumbs from sudden death, at autopsy, more attention to the possible coexistence of OSAS, dental malocclusion, subtle anomalies of the autonomic nervous system and cardiac conduction system should be given, in order to identify the triggering factors for sudden death.

One of the CCM investigators [22] has previously reported on seven autopsied patients, who died during the hospitalization in which they experienced delirium in the ICU. The principal neuropathological findings were consistent with hypoxic ischemia in several areas of the brain, but most significantly in the hippocampus (memory area) and pons (near the brainstem vital centers). Acute deficits in memory could certainly be consistent with delirium. Although these hypoxic ischemic injuries in the brain could easily explain the patients' death, there are other possible causes of death. Primary cardiovascular disease might be high on the differential after the last decade, when there has been a lot of research establishing a relationship between sleep deprivation and endothelial dysfunction/disease.

Sleep deprivation has been almost as well studied as ICU delirium, and the two have much in common. How could a patient sleep normally in the ICU with buzzers and beepers going off all the time, tubes in the throat, lights turning on and off—and nurses walking around, talking, and waking them up for hourly neuro checks? And endothelial dysfunction/disease may be a major contributor to coronary disease. Although the relationship between sleep deprivation and endothelial dysfunction/disease is well established by many investigators [23], its etiology is unclear. Many have implicated the autonomic nervous system [24]—and gravitational ischemia in the brain has even been suggested [2]. In conclusion, there is a need for future autopsy studies of ICU delirium patients who die, focusing on both the brain and the heart.

1. Summary

Patients who experience delirium in the ICU also experience a higher incidence of near-term mortality. Currently unexplored regarding ICU delirium is the role of gravity in the brain. The meninges and cerebrospinal fluid surrounding the brain may provide some cushioning, but do not mitigate the effects of gravity. In contrast, the heart and lungs are continuously in motion—and they are surrounded by soft tis-

sues. The solitary tract nucleus of the medulla with its limited watershed vascular capacity may occasionally be the focus of transient ischemia caused by the increased metabolic demands associated with frequent and intense neuronal stimulation from other organs and other parts of the brain—as would typically occur in an ICU setting. Case reports have suggested that these focal ischemic changes may sometimes result in the initiation of intense autonomic discharges, which can occasionally be fatal. On the other hand, detailed postmortem examinations of victims of sudden unexpected death have revealed in some cases no cause of death except for the presence of a brainstem lesion. Decreased arterial CO₂ in the brain causes vasoconstriction, which reduces blood flow and worsens ischemia in medullary autonomic nuclei. An abnormal neural discharge to the heart via dorsal motor nucleus of vagus nerve would follow, resulting in arrhythmias, altered vascular tone, and sudden death.

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