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Editorial
Published: 27 Sep, 2020

Journal of Forensic Medicine Forecast

Gravitational Ischemia Induced Neuronal Hypoxia may be a Primary Neurologic Disorder Causing Regional Brain Volume Loss as Well as Seizures-And may be a Precursor in Some Cases of SUDEP

Jaster JH*

Department of Medicine, London Corporation, London, United Kingdom

Keywords

Gravity; Ischemia; Brain; Adenosine; Seizure

Editorial

Medical investigators interested in problems relating to forensics have recently published three papers [1-3], through which valuable data and insight have been provided regarding the possible etiology of Sudden Unexpected Death in Epilepsy (SUDEP)-specifically from a stand-point of pathophysiology, including regional brain volume loss [1,2], adenosine [3], and hypoxemia related to compromised ventilation during seizure activity [1]. An earlier report [4] had addressed the strictly pathologic basis of the regional brain volume loss associated with SUDEP, including hypoxic neuronal changes, as well as numerous other pathologic findings in a group of SUDEP cases.

The development of regional brain hypoxia (decreased oxygen level in tissue) can be circuitous and complex [5-10]. It may occur in any of several different settings - anemia, carbon monoxide, decreased partial pressure of inspired oxygen (i.e. at high altitude), and decreased blood perfusion are only a few. Recent re-analyses of clinical trials [5-10] have made the unexpected observation that deaths occurring during sleep apnea treatment and during Cardio-Pulmonary Resuscitation (CPR) were in part related to decreased brain perfusion of vital centers. This was likely caused by vasoconstriction due to decreased brain carbon dioxide (CO_2) levels secondary to increased ventilation - rather than by hypoxemia (reduced partial pressure of oxygen in the blood).

Regarding SUDEP victims, the investigators [2] suggest that, 'Regional brain volume assessments in patients who succumb may allow determination of processes that contribute to the fatal event or fail to provide adequate compensatory recovery.' I agree. And in that context I would mention a generally under-recognized process, hiding in plain sight, which may 'contribute to the fatal event': gravity - or, more specifically, gravitational ischemia, caused by vascular compression. And this would, as well, support a model for a 'compensatory recovery' mechanism which may fail - the decompression and re-opening of brain capillary beds to allow reperfusion.

'Gravitational ischemia' relates to the mass effect of one part of the brain upon another in a gravitational field. 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. Regional gravitational ischemia develops on the bottom side of the brain, as a function of vascular compression and subsequently reduced blood flow. It may then become associated with tissue (neuronal) hypoxia in the corresponding geography (spatial distribution). A macro-analogy from obstetrics might be the mass effect of the uterus in pregnancy intermittently obstructing blood return to the heart through the inferior vena cava based on its position, resulting in hypotension - and consistent with the term 'gravid'.

Unknown local tissue-based physiologic pathways may allow restoration of blood flow by reopening local capillary vascular beds following repositioning (unloading of ischemic regions) of the brain relative to gravity - by head tilting, which is significant through the 24-hour sleep/wake cycle. These pathways may 'fail to provide adequate compensatory recovery' as a result of damage incurred by gravitational ischemia (or other causes) in susceptible individuals. In addition to its other roles [3], adenosine is a potent vasodilator released in the brain during seizures. Focal seizure activity may have itself been an imperfect primordial adaptive mechanism to induce local

Correspondence:
J. Howard Jaster, Department of Medicine, London Corporation, 17 Cheval Place, London SW7 1EW, United Kingdom.
E-mail: *harbert38104@yahoo.com*

Received Date: *09 Sep 2020*
Accepted Date: *19 Sep 2020*
Published Date: *27 Sep 2020*

Citation: *Jaster JH. Gravitational Ischemia Induced Neuronal Hypoxia may be a Primary Neurologic Disorder Causing Regional Brain Volume Loss as Well as Seizures-And may be a Precursor in Some Cases of SUDEP. J Forensic Med Forecast. 2020; 3(1): 1013.*

vasodilation in the brain capillary beds which failed to re-dilate after gravitational brain-mass re-positioning.

As a contributor to SUDEP, the compromised ventilation associated with seizure activity increases CO_2 levels and dilates brain vasculature, thereby increasing perfusion - making acute hypoxemia [1] less likely as a cause of death. As well, it is interesting to note that in a group of SUDEP cases, isolated neuropathologic observations include [4], 'These changes indicate a cerebral event occurring at least 4-6 h before death and are at odds with a "sudden" death which, by definition, occurs within 1 h.' And there is often no evidence of seizure activity at the time of death. This suggests that the findings may be more consistent with gravitational ischemia, which does not occur suddenly. The cumulative effects of acute intermittent hypoxemia related to seizures are, as well, an unlikely cause of neuronal hypoxia causing brain volume loss.

The constellation of data presented in these 4 papers [1-4] taken together may fit better into a model of gravitational ischemia, in which the bottom half of the brain incurs a weight burden created by the mass of the top half of the brain under the force of gravity. Whereas earlier re-analyses [5-10] of potentially relevant clinical trials have suggested that sudden deaths in different clinical settings were due to decreased brain perfusion related to CO_2 and vasoconstriction, this re-analysis suggests that SUDEP may, as well, be related to decreased perfusion - but here caused by vasocompression related to gravity. The commonality is an unrecognized source of vasoconstriction [5-10]/vasocompression [1-4] which reduces blood flow and subsequent tissue perfusion.

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