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Opinion

Acute Heart Failure, 90-day Mortality—and Gravitational Ischemia in the Brain

J. Howard Jaster [1] and Giulia Ottaviani [2,*]

[1] London Corporation, London SW7 1EW, UK; ORCID (JH Jaster): 0000-0001-5406-9554; harbert38104@yahoo.com
[2] Anatomic Pathology, Lino Rossi Research Center, Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, 20122 Milan, Italy; ORCID (G Ottaviani): 0000-0002-6982-170X
* Correspondence: Giulia.Ottaviani@unimi.it; Tel.: + 39-02-50320819; Fax: + 39-02-50320823.

Abstract: During the 90 days following hospitalization for acute heart failure, ejection fraction and type of discharge medications have been shown in clinical trials to have little effect on mortality. We examined the recent literature addressing brain-related etiologies of sudden death following heart failure. Two mechanisms of sudden unexpected death have been suggested to possibly result from 4 significant influences on pathophysiology in the brain. The two causes of death are severe cardiac arrhythmia, and neurogenic pulmonary edema. They are both mediated through the brainstem autonomic nuclei generally, and executed specifically through the dorsal motor nucleus of the vagus nerve. The four significant influences on pathophysiology in the brainstem autonomic nuclei are: 1) Hyper-stimulation of neurons in the solitary tract nucleus, increasing their metabolic requirements; 2) Inadequate blood flow at a vascular watershed terminus; 3) Additionally decreased blood flow following vasoconstriction related to relative hyperventilation and decreased pCO2 levels; 4) Gravitational ischemia in the brain—caused by the weight of the brain mass sitting above the brainstem. Changes in head tilt release gravitational ischemia in the brain. There is no specific head position (relative to gravity) that is considered favorable or unfavorable for an extended period of time (i.e. more than 24 hours). Even a small degree of head elevation, used in managing pulmonary congestion, may increase gravitational ischemia in the posterior fossa and brainstem. In this paper we suggest a new and important research avenue for intervening in cardiac arrhythmias, and preventing their occurrence, through the non-invasive use of head-tilting, and other head repositioning maneuvers. This could potentially help many geriatric patients with heart failure, who have decreased mobility in bed, and who tend to stay in one position longer, thereby increasing gravitational ischemia in the brain.

Keywords: Heart Failure; Gravity; Ischemia; Brain

1. Introduction

A multi-center group of Italian Investigators [1] recently evaluated patients with pulmonary and intravascular congestion at admission, as well as repeatedly during hospitalization, for acute decompensated heart failure. Patients with reduced ejection fraction (n=142) were compared to patients with preserved ejection fraction (n=172) using lung ultrasound and inferior vena cava ultrasound. This prospective study included 314 patients, mostly around age 80. Primary outcomes included death or re-admission to the hospital for heart failure at 90 days. Cogliati et al [1] reported that there was no significant difference in primary outcome between the two groups. They further suggested in their Abstract Conclusion that 'other factors beyond ejection fraction could play a role in congestion/decongestion patterns'.

The results of this study [1] echoed the results of another study reported by Spanish Investigators, just a few months earlier [2]. That study, as well, looked at heart failure

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patients—but only the subset with preserved ejection fraction, upon discharge from the hospital, specifically regarding their discharge medications. The Spanish Investigators compared the patient medication profiles with their primary outcomes of death or re-admission to the hospital for heart failure at 90 days. Specifically, they studied the use of anti-neurohormonal drugs, including beta-blockers, renin-angiotensin-aldosterone-system inhibitors, and mineral-corticosteroid-receptor antagonists. The patients were grouped as to whether they did (n=2,312) or did not (n=993) take any of these medications following discharge. This multi-center retrospective study included 3,305 patients, around 83 years old. The Spanish Investigators reported [2] that there was no significant difference in primary outcome between the two groups.

The results from both of these studies [1,2] may seem to defy logic. How can heart failure patients with poor ejection fraction [1] have the same 90-day mortalities as those with preserved ejection fraction? How can heart failure patients using medications known to improve hemodynamics and cardio-dynamics [2] not experience a benefit in 90-day mortality following hospital discharge?

Both of these questions may have been answered two decades earlier, by a group of Italian Neuroscience-Pathophysiology researchers [3], who studied five autopsy cases, comparing the brainstems of patients who died in acute heart failure. Their focus was the solitary tract nuclei, a component of the autonomic system, which receives messages about cardio-vascular and respiratory parameters from all over the body, mostly through the vagus network.

2. Discussion

2.1. Excitatory sensory ischemia, in a vascular watershed terminus

The Neuroscience Researchers discovered ischemia and infarctions in the brainstem, but limited to the solitary tract nuclei. They partly attributed this seemingly odd pattern to intense hyper-excitatory sensory neuronal input into the solitary tract nuclei during heart failure, which increased neuronal cellular metabolic requirements there [3]. They also cited the somewhat reduced blood flow to this region, which is anatomically located at the end of a water-shed area—and may be insufficient when metabolic requirements become very increased there.

These two factors taken together may have predisposed this area of the brainstem to ischemia—even in the absence of what is typically thought of as 'occlusive cerebrovascular disease'. Although subsequently cited dozens of times, the concepts outlined by the Neuroscience researchers [3] have probably been under-utilized in clinical practice as is possibly demonstrated by the two recent papers [1,2], neither of which mentioned the possible role of the brainstem. The concepts [3] additionally provided reasonable answers [4,5] to questions previously unresolved [6,7] regarding arrhythmia-induced sudden unexpected deaths related to small ischemic brain lesions in the medulla—the home of the solitary tract nucleus. Some day they may allow us to intervene non-invasively in medical management to improve outcomes by preventing cardiac arrhythmias generated in the brain.

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2.2. Carbon dioxide, gravity—and thinking like a skin nurse

More recently, two additional contributing bio-physical factors, acting on blood flow in the brainstem, have been suggested as having a significant clinical role in the setting of heart failure. They seem capable of triggering abnormal discharges from the dorsal motor nucleus of the vagus nerve—the major outflow component of the vagus system, among the brainstem autonomic nuclei. This may initiate severe cardiac arrhythmias.

These two additional factors are vasoconstriction in the brain related to carbon dioxide (CO_2) levels [8,9], and gravity in the brain [10–15]. These possibly have several clinical effects, but the one applicable here is sudden unexpected death, related to both cardiac arrhythmias and neurogenic pulmonary edema [10–15]—and possibly responsible for significant mortality in patients discharged from the hospital following acute heart failure.

CO_2 is a potent vasodilator in the brain, and reduced CO_2 levels typically cause vasoconstriction—thereby contributing to ischemia in brainstem autonomic nuclei [8,9]. CO_2 levels become decreased most frequently as a result of mechanical ventilation, or respiratory therapy. They may similarly become decreased during management of sleep apnea, a frequent co-morbidity of heart failure.

Then, there is gravity. 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 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 to a significant degree 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 [10–15]. 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 8 hours at night during sleep. Ischemia, which may form on the bottom layers, is reversible in its early stages (Figure 1).

In healthy individuals, the horizontal supine body positioning associated with sleep 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 [10–15].

Gravitational ischemia in the brain may potentially be 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. Skin nurses currently implement these changes around the clock, in hospitals around the world.

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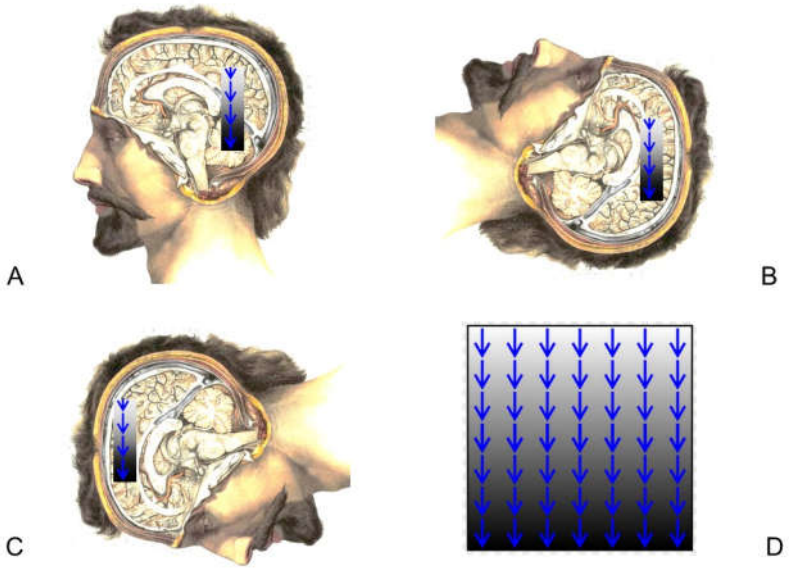

Figure 1.
A) Mid-sagittal view of brain in relationship to eye, face, and neck. Vertical (upright) position. Gravity (arrows) is pushing the cerebral hemispheres toward the brainstem and cerebellum.
B) Horizontal supine position.
C) Horizontal prone position.
D) Gravity. Schematic stratification of biological tissue into horizontally pancaking layers under the influence of gravity. Lower layers incur progressively increasing weight burden from upper layers, and thus increasing compression of blood vessels and reduction of blood flow, possibly resulting in regional ischemia.
Modified from Wikipedia; creative commons license. https://en.wikipedia.org/wiki/Human_brain#/media/File:Human_brain.jpg

2.3. Can the effects of gravity be seen on brain imaging?

Recently, a group of Welsh Investigators [16] reported that 'positional brain shift', the sagging of the brain under the effect of gravity, is significant, relative to the specific geometric coordinates generated by magnetic resonance imaging (MRI) for the purpose of guiding stereotactic surgery. If the guiding coordinates are generated by an MRI done in supine position, the brain will move slightly away from those coordinates, if the patient is placed into a different position for surgery. This was confirmed by studying 11 health young adult volunteers, who were specifically moved from supine position to prone, and back again [16].

Zappalà et al [16] concluded that slight non-uniform brain shifting due to differences in head orientation can lead to a significant discrepancy between the planned and the actual location of surgical targets. Additionally, strain analysis in their study revealed local variations in 'compressibility' within the brain. When horizontally rotating from prone position back to supine, the anterior regions showed expansion (with changes in both volume and shape), and the posterior regions showed 'compression', mostly dominated by changes in shape [16].

Given its low stiffness, brain tissue shifts occur within the cranial vault under the influence of gravity, due to changes in head orientation even in normal healthy individuals without any surgical intervention [16]. Zappalà et al [16] thus found that in

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repositioning young healthy adults from prone position to supine, the posterior fossa is compressed. This movement has a potential to compress brainstem autonomic nuclei, predisposing to ischemia formation there. Other changes in head positioning may have effects on brain shifting which are unexpected. Much more research is needed to quantify these, and their potential application to heart failure patients.

2.4. Spatial relationships of brain components

Another investigative group, out of King's College London [17], looked at the accuracy of MRI to document the spatial relationships of different parts of the brain relative to each other, and to consistently find those same relationships in a subsequent follow-up MRI performed at a later time, if in fact they were unchanged. They considered several variables like the 'make and model' of MRI machine, time interval between scans, and geographical placement of the patient on the surface of the scanner bed (i.e. slightly toward the starboard, port, bow, or stern)—as well as head tilting (pitch) relative to the scanner bed. They concluded that the only variable that caused a small but significant changes in the position of brain components relative to each other was head-tilting [17]. This is consistent with gravitational changes in the brain, which were not mentioned by the King's College Investigators.

In a second recent paper [18], the King's College Investigators looked at physiological parameters, such as relative dehydration, occurring diurnally, that might affect intra-brain structural relationships. They found none. However, they did not include time of day differences, which would reflect the sleep cycle, as well as the gradual diurnal development of gravitational ischemia.

2.5. Auto-regulation

Does auto-regulation play a role in this setting? Auto-regulation is a mechanism by which cerebral blood flow is maintained—primarily through regional vasoconstriction and vasodilation within the brain. It does not respond well to physical barriers such as intravascular clot or extravascular mass lesion. Gravity behaves as an extravascular mass lesion because it forces extravascular overlying brain tissue from above to 'push downward' against the external walls of the blood vessels. Reciprocally, it also forces underlying skull and meninges to 'push back upward' against blood vessels, causing them to be 'squeezed' between two forces. Another physical barrier, an intravascular clot, may similarly challenge the ability of autoregulation to maintain cerebral blood flow. Autoregulation often fails in that setting, resulting in the appropriately named 'cerebrovascular accident'.

Additionally, autoregulation is mediated largely through the brainstem autonomic nuclei. The MRI findings of the Welsh Investigators [16] suggested these may occasionally be compressed, and that ischemia there may be the likely result. While ischemic, they may lose their ability to function normally to maintain auto-regulation. And lastly, CO_2 changes may easily and immediately overcome cerebral autoregulation. A healthy adult who rapidly takes five deep breaths, will typically begin to experience light-headedness.

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3. Conclusions

1. During the 90 days following hospitalization for acute heart failure, two mechanisms of sudden unexpected death have been suggested to possibly result from 4 significant influences on pathophysiology in the brain.

2. The two causes of death are severe cardiac arrhythmia [4–7,12] and neurogenic pulmonary edema [13]. They are both mediated through the brainstem autonomic nuclei generally, and executed specifically through the dorsal motor nucleus of the vagus nerve.

3. The four significant influences on pathophysiology in the brainstem autonomic nuclei are:

a. Hyper-stimulation of neurons in the solitary tract nucleus, increasing their metabolic rate;

b. Inadequate blood flow at a vascular watershed terminus;

c. Additionally decreased blood flow following vasoconstriction related to relative hyperventilation and decreased pCO_2 levels;

d. Gravitational ischemia in the brain—caused by the weight of brain mass sitting above the brainstem.

4. Changes in head tilt release gravitational ischemia in the brain. There is no specific head position (relative to gravity) that is considered favorable or unfavorable for an extended period of time (i.e. more than 24 hours). Even a small degree of head elevation, used in managing pulmonary congestion, may increase gravitational ischemia in the posterior fossa and brainstem.

In this paper we suggest a new and important research avenue for intervening in cardiac arrhythmias, and preventing their occurrence, through the non-invasive use of head-tilting, and other head repositioning maneuvers using a hospital bed, and possibly other equipment. It could potentially help many geriatric patients with heart failure who have decreased mobility in bed, and who tend to stay in one position longer, thereby increasing gravitational ischemia in the brain.

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