

Phrenic Nerve Stimulation – and Chorda Tympani Nerve Stimulation – May Prevent Lethal Cardiac Arrhythmias During Sleep Apnea with Heart Failure

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ABSTRACT

Obstructive sleep apnea is associated with an increased risk of adverse cardiovascular events. Recently a large multi-national clinical trial studied patients with both obstructive sleep apnea and vascular disease to determine whether the addition of continuous positive airway pressure to otherwise ‘usual care’ was beneficial in preventing heart attacks, heart failure, unstable angina, and cardiovascular deaths during the subsequent 3.7 years. In the 8 September 2016 issue of the *New England Journal of Medicine* the Sleep Apnea CardioVascular Endpoints (SAVE) Investigators reported that it was not beneficial. This editorial in the *International Journal of Neurology Research* discusses the events and clinical trials leading up to the SAVE Trial report and discusses why they might easily have predicted the results obtained in the SAVE Trial. It also discusses a potential future direction for managing patients with sleep apnea and

cardiovascular disease. A component of that future direction may be phrenic nerve stimulation – the helpfulness of which now seems due to some reason other than simple ventilation of the lungs (which failed in the SAVE Trial and elsewhere). The mysterious ‘other reason’ may involve indirect electrical stimulation of the solitary tract nucleus by sensory and autonomic fibers in the phrenic nerve. Included in the future direction for managing sleep apnea patients may be computerized electronic stimulation of the chorda tympani nerve in the mouth – in an attempt to mitigate ischemic events in the solitary tract nucleus. This option would avoid the sometimes unwanted direct impact on respiratory muscles that comes with phrenic nerve stimulation – as well as the direct impact on the heart that comes with vagus nerve stimulation.

Key words: Sleep apnea; Heart failure; Sudden unexpected death; Vagus nerve stimulation; Brain dentistry; Chorda tympani nerve; Solitary tract nucleus; Phrenic nerve stimulation; Medulla oblongata

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BACKDROP – SUDDEN UNEXPECTED DEATH RESEARCH

Medical investigators in the 21st century have increasingly focused on neurotransmitter abnormalities in the medulla oblongata as the primary etiology of Sudden Infant Death Syndrome^[1] and also as the etiology of sudden unexpected deaths that occur in adults with Multiple System Atrophy^[2] – serotonin is the problem in both instances. Investigators have also reported numerous cases in which the presence of a very small anatomical medullary brain lesion, like a plaque of demyelinated white matter^[3], was associated with sudden unexpected death^[4,5] – and in all cases the lesions were without mass effect or hemorrhage^[6]. Many such medullary lesions have otherwise produced only minor clinical symptoms and have in themselves

been previously considered relatively harmless – in cases where they have been known to be present. Many victims have been considered healthy prior to sudden death, and the medullary brain lesions were often incidental discoveries at autopsy, with no other causes of death identified.

But such cases are uncommon across the broad scope of medicine, and they serve mostly as ‘clean cases’ to demonstrate the correlation between subtle medullary brain lesions (neurotransmitter, or anatomical) and sudden unexpected death. Much more common are the ‘dirty cases’ in which sudden unexpected death related to a medullary brain lesion occurs during the course of another illness like pneumonia or in the setting of some systemic illness like sarcoidosis that may involve the medulla as well as other parts of the body – and in which the relationship between sudden death and the medullary lesion is more challenging to definitively substantiate^[7,8]. Taken together all of these cases can be viewed as an iceberg. The few ‘clean cases’ are the tip of the iceberg. ‘Dirty cases’ comprise the large submerged portion of the iceberg.

PROBLEM – FAILED MAJOR CLINICAL TRIAL

Recently coming to attention in this regard is the clinical research population ‘sleep apnea with heart failure’. Several university hospitals worldwide have poured considerable resources into international clinical trials attempting to verify that nocturnally applied mechanical ventilation at home would improve clinical outcomes when added to guideline-based medical treatment in patients with sleep apnea and heart failure, largely by reducing life-threatening cardiac arrhythmias^[9,10]. The reports from these clinical trials revealed that the ventilation therapy that had been considered ‘standard care’ for years was at best unhelpful, and at worst even harmful.

Why didn’t it work?

The unrecognized culprits in this patient population were possibly medullary brain lesions – mostly pin-point-size ischemic lesions in autonomic nuclei. The researchers possibly navigated their clinical trial directly into the path of the above-mentioned large submerged ‘dirty-case’ portion of the iceberg of sudden unexpected death related to medullary brain lesions.

How so?

ISCHEMIC LESION FORMATION

A large number of the ‘dirty cases’ result from ischemic lesions which form in the medullary autonomic nuclei. They are typically formed because of increased metabolic demands resulting from the sometimes chaotic afferent ‘return-messaging’ from the heart, lungs, and arteries, via sensory visceral autonomic fibers of the vagus nerve traveling back to the brain’s ‘central receiving station’ for such messaging – the solitary tract nuclei of the medulla oblongata.

This return-messaging can sometimes be characterized as excitatory – and occasionally so much so that some investigators believe that the process of receiving the feedback can itself actually damage the solitary tract nuclei^[11,12]. During periods of physiological stress, such as during sleep apnea or heart failure, the excitatory return-messaging is believed to significantly increase metabolic activity in parenchymal tissue in dendritic areas of the solitary tract nuclei – and in the setting of limited perfusion from a limited watershed vasculature.

The resulting medullary ischemic lesions then often disrupt autonomic regulation enough to trigger violent autonomic discharges which are life-threatening^[6]. The specific mechanisms are unknown^[6], but a common clinical manifestation is severe cardiac arrhythmias^[6,11,12]. The failure of the various recent clinical trials^[9,10] to prevent life-threatening cardiac events possibly lies in their failure to address the focal physiological mis-match causing medullary brain ischemia^[11,12] – a mis-match which seems undeterred by the improvement of nocturnal systemic blood gasses.

What can be done?

THE POSSIBLE SOLUTIONS MAY SEEM SHOCKING

At this time, based on limited data, phrenic nerve stimulation^[13,14] is considered a useful therapy for sleep apnea with heart failure. Some of the reasons for this may be hiding in research data supporting the use of vagus nerve stimulation in the treatment of epilepsy. Many vagus nerve fibers travel efferently down-stream from the point of electrical stimulation toward the heart and other organs. And some clinical investigators have reported that vagus nerve stimulation in epilepsy patients has reduced cardiac electrical instability^[15] — a potential trigger for lethal arrhythmias — probably by a down-stream mechanism. But many sensory autonomic fibers of the vagus nerve begin in the chest and abdomen and travel afferently up-stream to terminate in the solitary tract nucleus in the medulla. Vagus nerve stimulation also follows those afferent up-stream fibers toward this critical area, and then apparently goes on to stabilize electrical activity throughout the cerebral cortex to prevent seizure activity by a mechanism yet unknown. Vagus nerve stimulation indirectly stimulates the solitary tract nuclei, where it increases blood flow locally^[16]. Phrenic nerve stimulation was developed to elicit purposeful muscle contractions in specific muscles of respiration to enhance breathing, but its efficacy may ultimately be shown to be more related to other factors like indirect electrical stimulation of the medulla – and the failure of mechanical ventilation in the treatment of ‘sleep apnea with heart failure’^[9] might tend to support this.

The phrenic nerve is primarily a motor nerve to the diaphragm, but it carries both sensory and autonomic fibers as well. Electrical stimulation of the phrenic nerve may have stabilizing influences on the solitary tract nuclei through several remote neural connections. And counter-intuitively there may one day be a role for vagus nerve stimulation in patients with respiratory sleep disorders, despite its lack of motor innervation relevant to breathing. Electronic stimulation of the vagus and phrenic nerves, individually or in combination, may ultimately prove to be helpful in modulating or preventing lethal autonomic disruptions and cardiac arrhythmias associated with ischemic autonomic nuclei in the medulla oblongata, just as vagus nerve stimulation reduces seizure activity^[17].

VAGUS NERVE STIMULATION FAILED IN ‘HEART FAILURE CLINICAL TRIAL’

Basic research in animal models has mostly been focused on the efferent down-stream effects of vagus nerve stimulation on the heart, and it continues to provide results which encourage its use in heart failure^[18]. However, the recent report of a clinical trial^[19] revealed that vagus nerve stimulation was unhelpful in reducing all-cause mortality in a cohort of heart failure patients. The reasons for this failure, though unknown, are likely related to the efferent down-

stream effects of vagus nerve stimulation on the heart and other organs, rather than the afferent up-stream effects on the solitary tract nuclei. And vagus nerve stimulation may still have a significant role in the management of patients with medullary brain lesions, or sleep apnea, who do not have heart failure.

VAGUS NERVE STIMULATION FAILED TO REDUCE SUDEP IN CLINICAL TRIALS

Sudden unexpected death in epilepsy (SUDEP) is a relatively common adverse effect of chronic intermittent seizure activity – considered by some to possibly be caused by abnormal bursts of electrical autonomic activity likely involving the medullary autonomic nuclei. Although it might reasonably be hoped that the characteristics of vagus nerve stimulation which disrupt seizure activity would also disrupt the abnormal autonomic activity causing SUDEP, the results of clinical trials suggest otherwise^[20].

The reason for the discrepancy may be related to the efferent down-stream effects of vagus nerve stimulation on the heart and other organs – as was the case in heart failure patients, even though epilepsy patients do not typically have heart disease. But this might potentially suggest that some fraction of individuals with abnormal electrical circuitry in the brain, manifesting as epilepsy, also have abnormal electrical circuitry in the heart – and that these individuals are susceptible to SUDEP. The afferent up-stream effects of vagus nerve stimulation on the brain may reduce the susceptibility to seizures while its efferent down-stream effects on the heart may exacerbate its susceptibility to lethal arrhythmias – and even trigger them.

BRAIN DENTISTRY

These dilemmas call for a solution that will remedy the electrical instability of the solitary tract nuclei caused by ischemic lesions – without causing the excessive down-stream cholinergic stimulation of vagus nerve stimulation on the heart. And to that end, one recent report^[17] proposed a futuristic therapy called ‘brain dentistry’ – a yet untried but plausible use of implanted molar modules containing computer chips to provide electronic stimulation of the chorda tympani nerve in the mouth, which – just as the vagus nerve in the chest – travels directly to the solitary tract nucleus of the medulla.

Brain dentistry would stimulate the chorda tympani nerve via a submucosal wire from the molar module to a site at or proximal to where the chorda tympani nerve runs together with the lingual nerve – a site frequently used by dentists for the injection of local anesthetic agents to anesthetize one side of the tongue together with the adjacent gingiva when performing procedures on the mandibular teeth^[17]. The chorda tympani nerve mediates taste sensation from the anterior 2/3 of the tongue, and is largely an innocent bystander for purposes of the dental injection.

Stimulation of the chorda tympani nerve indirectly stimulates the rostral third of the solitary tract nucleus of the medulla via functional connections, just as vagus nerve stimulation indirectly stimulates the caudal 2/3 of the solitary tract nucleus^[17]. Some of the potential general goals of brain dentistry would be to provide neural protection to vital centers of cardiac and respiratory function and to enhance their performance by optimizing blood flow, preventing ischemic injury, and supporting electrical stability.

Brain dentistry may also have a significant role in monitoring. And the potential usefulness of brain dentistry in the patient population that typically receives molar dental implants may at some future

time be sufficient to include some level of computerization of those implants as ‘standard equipment’.

SUMMARY

Indirect computerized electronic neuro-stimulation of the solitary tract nucleus via the vagus nerve and via the chorda tympani nerve may promote electrical stability in the autonomic nuclei of the medulla oblongata, thereby reducing the incidence of severe discharges which manifest clinically as life-threatening cardiorespiratory events in patients with medullary brain lesions or with significant susceptibility to ischemic lesion formation. Stimulation of the phrenic nerve may potentially be used to achieve the same goals by indirectly stimulating other medullary nuclei – in clinical settings where its motor functions are considered beneficial.

TESTING

Vagus and phrenic nerve stimulation can potentially be used ‘off-label’ in varied stimulation parameters to study patients with known medullary lesions, or who are at risk for ischemic lesions. Both are already otherwise used in clinical practice and their general safety profiles have been established.

Testing of brain dentistry will be more difficult, but can be broken down into its components. Short-term stimulation of the chorda tympani nerve without a molar module can potentially be accomplished using some version of small floating microelectrical stimulators^[21], implantable wireless neural stimulators^[22], or neuro-monitors^[23] – initially in appropriate animal models.

More autopsy studies of the medulla are needed to better characterize the details of ischemic autonomic lesions. Methods of studying the circulation and metabolic activity of individual medullary nuclei during life are needed as well. This is a greater challenge in as much as the medulla is relatively small and inaccessible.

THE SHOCKING FUTURE

By the year 2050 a common admitting diagnosis in the intensive care unit – in the context of a variety of medical conditions – may be ‘Acute Solitary Tract Nucleus Insufficiency’. In 2050 chorda tympani nerve stimulation may be a component of acute management – or only chronic maintenance therapy – or neither. At this time no one knows. Our challenge during the coming years is to find out.

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