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The proposed use of cervical spinal cord stimulation for the treatment and prevention of cognitive decline in dementias and neurodegenerative disorders

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ABSTRACT

Cervical spinal cord stimulation is a well-established treatment for intractable neuropathic upper extremity pain. More than 20 years ago it was demonstrated that cervical spinal cord stimulation could engender an increase in cerebral blood flow. Cerebral blood flow has been shown to be decreased in many patients with dementia and in various neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Furthermore, there is evidence that reduced cerebral blood flow worsens neurodegenerative disease and may also predict which patients progress from mild cognitive impairment to full blown Alzheimer's disease. Thus, the identification of decreased cerebral blood flow in patients with early cognitive problems may offer clinicians a window of opportunity to intervene and prevent further brain damage. Further evidence that supports augmenting cerebral blood flow as an effective strategy for preventing and treating cognitive brain dysfunction comes from experimental studies with omental transposition. The author proposes cervical spinal cord stimulation as a titratable, programmable extracranial neuromodulation technique to increase cerebral blood flow for the purposes of improving cognitive function and preventing cognitive deterioration in patients with dementias and neurodegenerative disorders.

Background

Spinal cord stimulation (SCS) is a well-established surgical modality that involves implantation of epidural electrodes, connecting wires, and pulse generators to achieve chronic electrical stimulation of the spinal cord. The primary indication for SCS in the United States remains chronic pain, particularly that resulting from failed back surgery syndrome or complex regional pain syndromes [1–5]. Although the analgesic mechanism of SCS remains a matter of debate, several theories have arisen to explain why electrical stimulation of the dorsal column fibers within the spinal cord can alleviate chronic pain, particularly neuropathic pain [6–8].

SCS is usually performed in the thoracic spine to treat lower extremity and axial back pain. Less frequently, SCS is performed in the cervical spine to treat pain syndromes involving the neck and upper extremities [9–11]. In Europe, the most frequent indication for SCS remains extremity pain secondary to peripheral vascular disease (PVD). Several reports have shown that SCS can engender regional vasodilation, which may make it particularly effective for patients with PVD-associated pain [12–14]. The leading theories behind SCS-induced vasodilation argues that vasodilation occurs secondary to either a reduction in sympathetic nervous system activity (i.e. "functional sympathectomy") or from the release of vaso-active substances such as calcitonin gene related peptide and nitric oxide [15–17]. This vasodilatory effect of SCS has also been exploited in the treatment of refractory angina pectoris, in which SCS has been shown to not only reduce anginal pain but also to increase myocardial perfusion [18–21].

First recognized by Hosobuchi in 1985, cervical SCS has been shown via both animal and human studies to increase cerebral blood flow (CBF) [22–25]. Specifically, more than one group has demonstrated that high cervical SCS (C1-3) at moderately low frequencies (20 Hz), but not low cervical SCS or thoracic SCS, increases CBF [24,26–28]. The mechanisms behind SCS-induced augmentation of CBF remain under investigation, however there is considerable evidence that SCS acts via the sympathetic nervous system [16,29,30]. Chemical blockade of sympathetic ganglia with hexamethonium and alpha-1-adrenergic receptor inhibitors can suppress the increase of CBF engendered by SCS [27,31]. SCS-induced CBF augmentation does appear to require dorsal column input to the brain since spinal cord transection and dorsal column section can abolish the response [26,32].

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Hypothesis

My hypothesis is that augmentation of CBF by commercially available high cervical SCS may be useful for the treatment and prevention of cognitive decline in various dementias and neurodegenerative diseases such as Alzheimer's disease.

Evidence for cerebral hypoperfusion and cognitive impairment

Decreased CBF or cerebral hypoperfusion has been correlated with cognitive decline secondary to both normal aging and to neurodegenerative disorders. Cognitive function, especially as measured by speed of information processing, attention, dual task performance, and memory, declines with age. In addition to being associated with atrophy of the gray and white matter in the brain, this age-related cognitive decline has been shown to be associated with a decrease in CBF [33,34]. In fact, multiple studies have revealed a continuous decrease in resting CBF in the global gray matter of the brain during adulthood and other studies have measured specific regional decreases in resting CBF with increasing age [35–37]. Moreover, there are several lines of evidence directly linking CBF with cognitive performance in normal adults. For instance, in a study of elderly participants aged 62–85 years, Rabbitt et al. demonstrated a negative correlation between resting carotid and basilar blood flow and tests scores in several cognitive tasks [38]. In another study which quantified CBF using continuous arterial spin labeling magnetic resonance imaging, Bertsch et al. showed a negative relationship between resting CBF and attention task performance in both young and elderly healthy individuals [39]. Heo et al. found that increased blood flow to the hippocampus was associated with better memory performance in older adults [40]. Finally, there is evidence that cerebral hypoperfusion predicts later cognitive decline in cognitively-intact adult patents [41].

In addition, decreased CBF has been associated with worse cognitive function in patients with dementia and neurodegenerative diseases and may predispose patients to rapid progression. In an important study using SPECT to quantify CBF, Hirao et al. found that reduced CBF in the several parts of the brain including the inferior parietal lobule, angular gyrus, and precunei had a high predictive value in demonstrating which patients with mild cognitive impairment (MCI) would go on to develop full-blown Alzheimer's disease (AD) [42]. Another study found that patients with MCI who ultimately developed AD had a significant reduction in blood flow to the posterior cingulate gyrus which could be found at least two years before the development of AD [43]. Brain perfusion SPECT in another study of patients with AD found that decreased blood flow to the frontal lobe correlated with reduced cognitive function at the time of the evaluation as well as rapid progression [44]. Thus, the term neurodegenerative as a label for diseases such as AD may be misleading in the sense that it suggests an inexorable, programmed path toward progression. There are now multiple lines of evidence to suggest that decreased CBF precedes decline in patients ultimately diagnosed as having AD, and the detection of cerebral hypoperfusion with modern neuroimaging immediately suggests a window of opportunity to intervene and prevent cognitive dysfunction secondary to chronic brain hypoperfusion.

Cerebral hypoperfusion has additionally been identified as a characteristic of other dementias and other so-called neurodegenerative disorders. For example, patients with Parkinson's disease with dementia show decreased CBF in the left temporo-parietal lobe of the brain as compared to Parkinson's disease patients without dementia [45]. In a study of several different types of human dementia, all patients with dementia were found to have hypoperfusion of the left superior frontal lobe of the brain [46]. The cognitive dysfunction associated with depression ("pseudo-dementia") has also been found to be associated with cerebral hypoperfusion [47]. The cognitive function of patients with other brain diseases including normal pressure hydrocephalus, brain tumors, subarachnoid hemorrhage, and traumatic brain injury has also been shown to parallel CBF; higher mean CBF correlated with higher neuropsychological test scores [48].

Cerebral hypoperfusion is not solely an epiphenomenon of dementias and neurodegenerative disorders and there is growing evidence that treatments associated with increasing CBF can improve cognitive function. For instance, in a study of older adults undergoing cognitive rehabilitation, the cognitive training program improved both cognition and resting CBF to the prefrontal cortex as compared to controls [49]. Donepezil, a drug used to treat the cognitive dysfunction of Alzheimer's disease, increases CBF in responders but not in non-responders [50]. The molecule resveratrol, a natural polyphenol found in red wine, has been linked with improved cognition and increased CBF in both human and animal studies [51,52]. The cognitive improvement seen in patients with normal pressure hydrocephalus treated with ventriculoperitoneal shunting has also been associated with increasing CBF [53,54].

Further evidence that supports augmenting CBF as an effective strategy for preventing and treating cognitive brain dysfunction comes from studies of omental transposition. The omentum is a layer of vascularized fat that covers and protects the intra-abdominal organs. Omentum transposition is a surgical procedure that may be used to increase blood flow to an organ such as the brain. There is evidence from small studies that transplanting portions of pedicled omentum onto the brain of patients with AD may improve CBF ipsilateral to the omentum-covered brain hemisphere, cognitive scores, and reduce senile plaque burden [55–62]. The omentum is thought to increase CBF by promoting angiogenesis or new blood vessel growth into the brain. In a study of six biopsy-confirmed cases of AD, omental transposition engendered statistically significant cognitive, functional, and behavioral improvements for up to 3.5 years in the patients; in fact, compared to randomized trials of cholinesterase inhibitor medications for AD, omental transposition was 34 times more likely to produce clinically significant improvement [63]. A prospective, single-arm, non-randomized study of omental transposition for early AD is currently enrolling subjects in the United States [64]. Despite the promising results of this CBF-augmentation surgery for cognitive disorders such as AD, omental transposition requires both a craniotomy and laparotomy/laparoscopy and carries significant perioperative moribidity such as seizures. Unlike omentum transposition which may be used to increase regional hemispheric CBF, cervical SCS is proposed as a less invasive way to augment CBF in a global and titratable fashion.

Clinical evidence of cervical SCS in other cerebral hypoperfusion states

Cervical SCS has already been performed in humans to increase CBF and alleviate symptoms in other disorders. Patients with symptomatic cerebral ischemia from vertebrobasilar and carotid artery occlusive disease [65–67] as well as cerebral vasospasm [68–71] which occurs after aneurysmal rupture have been treated with cervical SCS to augment CBF. In addition, cervical SCS is currently being explored in patient with malignant brain tumors. It is thought that decreased CBF in high-grade gliomas makes such tumors resistant to both radiation and chemotherapy. Preliminary data has shown that cervical SCS may be able to modify locoregional blood flow in high-grade malignant tumors of the brain [72–74]. Although the clinical benefits of cervical SCS in these diseases remains to be determined, these studies have established