Commentary

Interfacing pathophysiology of respiratory sleep disorders, cardiac dysfunction, and focal autonomic medullary brain ischemia

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In recent months two review articles (1,2) in the journal have discussed respiratory sleep disorders (RSD) in regard to their cardiac complications, their pathophysiological interactions with heart disease, and their relationship to dysfunction of the autonomic nervous system.

Naughton begins his abstract (1) by noting that "*RSD occur in about 40–50% of patients with symptomatic congestive heart failure (CHF). Obstructive sleep apnea (OSA) is considered a cause of CHF, whereas central sleep apnea (CSA) is considered a response to heart failure, perhaps even compensatory.*" On page 1,301 he mentions that "*CHF may result in fluid retention and deranged autonomic control. Deranged autonomic control (heightened sympathetic and diminished vagal tone) is thought initially to be compensatory for the low cardiac output.*"

Stansbury and Strollo (2) on page E300 noted that "*Arrhythmias, particularly atrial fibrillation, have been well-documented in the OSA population and are likely consequences of respiratory abnormalities and changes in autonomic tone during sleep. Contemporary case-control and cross-sectional studies as well as studies dating back 30 plus years support the relationship between OSA and cardiac arrhythmia (references). The rhythm disturbances documented in these studies include ventricular tachycardia or fibrillation, sinus arrest, atrioventricular conduction blocks, complex ventricular ectopy, supraventricular tachycardia, bradycardia, and atrial fibrillation (references).*"

These interactions, which are complex and poorly understood, are beginning to interface with reports in the neurology (3), neuropathology (4), and forensic (5) literature which describe small ischemic medullary brain lesions in patients who died following a period of illness. Some of these deaths were anticipated, such as those following acute heart failure lasting several hours to several days (3). In other cases death occurred suddenly and unexpectedly as in patients with CSA (4). In such reports the very small areas of ischemia or infarction were localized within the brain medulla specifically to the solitary tract nuclei, which are supported mostly by a watershed vasculature and are subjected to increased metabolic demands associated with their reception of excitatory visceral sensory input from thoracic organs and elsewhere during such illnesses as heart failure and sleep apnea. These small lesions in turn seem capable of triggering life-threatening autonomic discharges by mechanisms which are largely unknown (5), but which certainly include cardiac arrhythmias.

The implications for patient care are not inconsequential. Naughton (1) mentioned in his abstract that "*Whether adaptive servo controlled ventilatory support, a variant of CPAP, is beneficial is yet to be proven.*" Subsequent to his paper, Cowie *et al.* (6) reported that it was not beneficial for their study patients with sleep disordered breathing and cardiac disease. The reasons for this failure of therapy (6) are unclear. Yet improvement of nocturnal systemic blood gasses (6) probably has little overall effect on the focal physiological mis-match implied by the neuropathology reports (3,4) of ischemic medullary brain lesions associated with heart failure and sleep apnea.

An alternative therapy under investigation is phrenic nerve stimulation. A recent international trial of only 57 patients with CSA who received unilateral phrenic nerve stimulation (7) showed that it was both safe and effective, even for those who also had heart failure. The apparent discrepancy between the inefficacy of purely mechanical therapy (6) and the efficacy of neuro-electronic therapy (7) may be reconciled in part by research done regarding vagus

nerve stimulation, which has been successfully used in the treatment of epilepsy—and in epilepsy patients it has also been shown to increase blood flow in the medulla as well as in other areas of the brain (8).

Many sensory autonomic afferent fibers of the vagus nerve begin in the chest and abdomen and terminate in the solitary tract nucleus in the medulla. Vagus nerve stimulation follows those fibers to 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. Other research (9) has shown that vagus nerve stimulation has some potential to stabilize cardiac electrical function. Although primarily a motor nerve (to the diaphragm), the phrenic nerve carries both sensory and autonomic fibers as well. Phrenic nerve stimulation may possibly have a modulating and stabilizing effect on medullary autonomic nuclei, which might help to prevent adverse cardiac events and improve patient outcomes.

Another neuro-electronic therapy, hypoglossal nerve stimulation (HNS), was recently reviewed in the Journal by Pengo and Steier (10). In their abstract they noted that "*Electrical stimulation (ES) of the upper airway (UAW) dilator muscles for patients with obstructive sleep apnoea (OSA) has been used for several decades,…*", and that "*HNS leads to a significant reduction in the apnoea-hypopnoea index and the oxygen desaturation index (ODI).*" In the medulla oblongata the hypoglossal nucleus is a nearby neighbor of the solitary tract nucleus, with which it shares some connections.

Future research in cardiac dysfunction with RSD probably needs to involve the medullary autonomic nuclei in the brainstem as well as thoracic organs, muscles of breathing, airway maintenance, and systemic blood gasses. Counter-intuitively there may one day be a role for vagus nerve stimulation in patients with RSD, despite its lack of motor innervation relevant to breathing. And perversely, future research may show that at optimal stimulation parameters, HNS can be a very effective therapy—but largely because it stimulates the hypoglossal nucleus of the medulla oblongata by retrograde nerve conduction.

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Footnote

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