COMMENTARY

Vagal Afferent Stimulation as a Cardioprotective Strategy? Introducing the Concept

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The effect of vagal afferent signaling on cardioinhibition has been well known for over 130 years. Both experimental and clinical studies have demonstrated not only the potential adverse effect of unrestrained sympathoexcitation in high risk patients with ischemic heart disease but the potential for cardioprotection by programmed vagal activity. The vasodepressor and negative chronotropic effects of efferent vagal stimulation has been a cause for concern. However it is becoming clear that favorable shifts towards increased cardiac vagal modulation can be achieved by vagal afferent nerve stimulation. This phasic effect appears to operate through central medullary pathways. Thus by engaging vagal afferent fibers in humans there is the possibility that one can exploit the benefits of central cardioinhibition without adversely affecting heart rate, respiration or hemodynamics. This commentary explores the background and rationale for considering vagal afferent stimulation as a plausible cardioprotective strategy.

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In the late 1920s, W.B. Cannon coined the term "homeostasis" to describe a tightly integrative process governing physiologic systems.¹ This concept, akin to Claude Bernard's more encompassing "milieu interieur," visualized the body's regulatory networks as somehow "rheostating" about optimized set points. Today, we are apt to reinterpret "homeostasis" as less a constraint than a dynamic balance between positive feed-forward systems (unfettered sympathoexcitation) and inhibitory (negative feedback) systems.² From a neurocardiology perspective, this balance not only offers needed slack but operates hierarchically at multiple sites; i.e., centrally within the central nervous system (CNS)^{3,4} and peripherally at (1) the level of spinal cord reflexes⁵ and (2) neuroeffector organs.⁶

Let us take an example. When central command is called upon in preparation for physical exercise, a positive feed-forward rush of sympathetic neural discharge results in a concomitant increase in blood pressure and heart rate. Such a parallel rise is antithetical to the concept of a fixed set point or gain in arterial baroreceptor function. And yet, allowance is made to shift the gain temporarily before it is reconstituted or modulated by negative feedback cardioinhibition. A major site for this

inhibitory brake is the nucleus tractus solitarius (NTS), a medullary relay station that receives multiple vagal afferent inputs critical to cardiorespiratory regulation. Within the NTS a complex set of neural interactions serves as a central processor that helps modulate the short-term give and take between efferent cardiosympathetic and cardiovagal activity.^{7,8}

AFFERENT SIGNALING AND CENTRAL PROCESSING

Vagal afferents innervate receptor sites serving diverse viscerosensory functions. Among these are: low-pressure baroreceptors integral to volume regulation; arterial baroreceptors that mediate short-term adjustments in systemic blood pressure; pulmonary and thoracic stretch receptors that contribute, in part, to phasic changes in sinoatrial function; chemoreceptors that sense changes in arterial blood gases; unmyelinated ventricular C fibers that elicit reflex vasodilatation; and unspecified receptors whose ascending pathways are antinociceptive.

Activation of these receptors, be they chemical, mechanical, or otherwise, generates tonic impulses

that are fundamentally inhibitory to central sympathetic neural discharge.⁹ In the NTS these vagal afferent signals undergo a complex series of mono- and polysynaptic interactions involving either/both excitatory (glutamate) and inhibitory (GABAergic) transmission.¹⁰

From this "black box" impulses are projected to other CNS relay stations¹¹ including the thalamus and forebrain (vigilance, perception, and behavior); the nucleus ambiguus to awaken dormant vagal efferent neurones; the dorsal motor horn to excite vagal efferent discharge and the rostral ventral lateral medulla to powerfully inhibit noradrenergic containing sympathetic neurones. Within this tangle there may lurk a "homeostatic" message but, even conceptually, we have barely scratched the surface. Is there a plausible model? Yes. But first, an historical interlude.

The effect of afferent signaling on cardioinhibition has been known since 1867 when von Bejold and Hirt observed a reflex vasodepressor response to chemical stimulation of cardiac sensory nerve endings.¹² In the late 1970s, the afferent limb of this inhibitory reflex was discovered to be unmyelinated C fibers.^{13,14} By the early 1990s it was already recognized that vagal afferent stimulation inhibits efferent sympathetic outflow by way of brain stem vasomotor circuits.¹⁵ As far back as the 1960s it was established that sympathetic neuronal discharge is intimately affected by baroreceptor inputs.¹⁶ Throughout the 1980s and 1990s evidence was established for relays in mid-brain nuclei that modulate vagoafferent inhibition of spinal nociceptive transmission.^{17,18}

In the 1980s, it became apparent that the cardiac and respiratory control systems, while seemingly interdependent, were, in other respects, separate. Eckberg has drawn attention to the manner in which the phasic nature of respiration (sensory input) "gates" cardiac neural outflow by modifying preganglionic vagal and sympathetic motoneurons.¹⁹ However, it is now acknowledged that the amplitude of respiratory sinus arrhythmia does not necessarily reflect proportional changes in parasympathetic control.^{16,20} Central mechanisms can produce the phasic pattern of sinus arrhythmia independent of respiratory stretch receptors or lung inflation.^{21,22} This suggests a central "need" for phasic patterning independent of peripheral signaling. Despite these developments we somehow persist in using the terms "tonic" and "phasic" interchangeably.

MAKING SENSE OF THE PHASIC VERSUS TONIC IMBROGLIO

We may or may not be born with our brain hard wired in the time domain but we certainly think and act like it! It is one thing to draw inferences from selective nerve recordings and another to step back and appreciate the Gestalt of neuroeffector responses. The latter is conveniently displayed mathematically by deconvoluting the hidden rhythms in the heart rate record.

For instance if, under steady-state conditions, one were to record a run of electrical impulses from tonically active vagal or sympathetic efferent nerves to the sinoatrial node one would see a repetitive discharge frequency oscillating about a "mean" value. This value essentially defines the average heart rate. If however, one took a step back one would be able to appreciate the variations (variance) in instantaneous heart rates as a function of its specific frequencies; i.e., a phasic phenomenon defined as a power density spectrum revealing well-defined spectral bands or oscillations.^{23,24}

These spectra have physiologic significance in so far as they represent modulatory or "phasic" processes fundamental to the control of sinoatrial function.²⁵ Let us assume that this phasic pattern originates, in part, from integrative circuits active within mid-brain centers such as the NTS. We know that the output signals from this "black box" can be both tonic and phasic.²⁶ And yet, they often bear little or no proportionality to individual tonic afferent input signals.²⁷ This implies nonlinearity in the reflex transduction from afferent to efferent signals.

The amplitude and periodicity of synchronized nerve discharges are independently regulated by afferent inputs. For instance, stimulation of right cardiac vagal afferent receptors inhibits cardiac sympathetic activity by reducing amplitude rather than the rate of synchronized discharge.²⁸ Baroreceptor stimulation appears to shift the phase relationship between cardiac vagal and sympathetic activity without altering the amplitudes of their respective oscillations.²⁹

In 1983, Ammons et al. reported that stimulating the left thoracic vagal nerve in anesthetized monkeys reduced the frequency of discharge from sympathetic neurones without necessarily affecting amplitude.³⁰ This effect was abolished by bilateral cervical vagotomy. Using tonic stimulation of the cardiac ends of vagal and sympathetic fibers,

Bailey et al. demonstrated significant changes in heart rate proportional to the intensity of stimulation of either vagal or sympathetic nerves.³¹ There was, however, no correlation between stimulus intensity and the phasic pattern represented by heart rate variability. Thus the power density spectrum of heart rate variability, a linear construct of a phasic or modulatory control system, need not necessarily correlate with nor be influenced by the "level" of efferent vagal or sympathetic tone.

In an interesting series of experiments, Hedman et al. challenged the concept that the high-frequency (HF) spectral component of heart rate variability is a manifestation of tone and modulation.³² They applied both phasic and tonic stimulation to the distal cut ends of cardiac vagal and left inferior cardiac nerves of anesthetized dogs. During constant tonic stimulation of the cardiac vagal nerve, heart rate decreased but there was no phasic variation in the beat-to-beat heart rate rhythm. Conversely, when the magnitude of the phasic pattern of stimulation was exaggerated, the heart rate variability increased proportionately but the mean heart rate remained unchanged. Furthermore, they observed that the magnitude of variation decreased as the frequency of sympathetic nerve stimulation increased. The higher the modulation frequency, the lower the amplitude. In other words at higher oscillatory frequencies, heart rate control became more tonic.³³

It seems clear that central processing is capable of generating highly differentiated neural outputs independent of the nature of individual tonic afferent inputs. It was not until we recognized the physiological correlates of these hidden heart rate rhythms that we began to reorder our thinking about cardiac regulatory mechanisms. The terms "tonic," and "phasic" therefore are mutually exclusive and should not be used interchangeably.

We may safely infer that the HF component reflects the magnitude of modulation of parasympathetic outflow rather than the tone (i.e., mean level of vagal activity). It follows that one should be able to achieve a cholinergic response by modulating vagal nerve output in addition to, and separate from, simply increasing the tone. One potential advantage of such a maneuver is a less dramatic fall in heart rate.

These observations raise several intriguing clinical questions. Is it possible and practical to achieve a more favorable shift in sympathovagal balance without altering heart rate or hemodynamics ap-

preciably? Can access to central relay circuits in the mid-brain be achieved by way of vagal afferent stimulation in humans? Is there a case to be made for vagal cardioprotection?

THE CLINICAL CASE FOR VAGAL PROTECTIVENESS

Experimental Studies

There is little dispute that sympathetic overactivity predisposes the ischemic myocardium to malignant arrhythmias. Does the converse hold? Namely, does sympathetic neural inhibition by vagal stimulation (either efferent or afferent) offer protection against ischemia-induced ventricular fibrillation? A number of studies have already confirmed that electrical stimulation of the right cervical vagus in dogs prevents ventricular fibrillation during ischemia. These observations have been validated for both anesthetized³⁴ and conscious animals.³⁵ However, the vagal nerve fibers stimulated in these studies were probably efferent judging from the significant decreases in heart rate observed.

There is a paucity of studies using selective vagal afferent stimulation on sympathetic efferent discharge. In an interesting series of experiments on rats, it was observed that activation of cervical vagal afferent fibers inhibits spinal dorsal horn sympathetic neurones mediating nociceptive reflexes.^{17,36} Feliciano and Henning have shown that vagal nerve stimulation in anesthetized dogs releases vasoactive intestinal peptide, an agent that dilates coronary arteries and increases coronary blood flow.³⁷

Clinical Studies

It has been appreciated for some time that patients with advanced heart disease have impaired vagal "tone."³⁸ There is an abundance of evidence, albeit indirect, that support a protective role for enhanced cardiac vagal activity. In an oft-cited study, Kleiger et al. showed that the lower the variance of the beat-to-beat heart rate record (a manifestation of suppressed vagal activity), the higher the risk of sudden cardiac death within 1 year of an acute myocardial infarction.³⁹

The beneficial protection of beta-blockers in post-MI patients is well known. What is less well-known is that the greatest benefit attributed to beta-blockers accrues to their protection against sudden

cardiac death.⁴⁰ Moreover, in addition to their pharmacologic effect as competitive inhibitors of beta-adrenergic receptors, beta-blockers are purported to enhance vagal activity.⁴¹

As for any cardioprotective benefit of direct vagal stimulation in humans, only scattered unsubstantiated accounts exist. Of historical interest it was more than 35 years ago that the carotid sinus nerve stimulator was first introduced as a therapeutic option for intractable angina.⁴² This procedure had teething problems related to technical issues, side effects, and unacceptable bradyarrhythmias. Besides, the procedure was "out-marketed" by coronary artery bypass surgery that was introduced, with great fanfare, at the same time. The concept is partly resurrected with the introduction of spinal cord stimulation for intractable angina.⁴³

From a pharmacologic perspective, some investigators have exploited the paradoxical vagomimetic properties of certain atropine derivatives. Transdermal scopolamine, when applied to patients with heart failure⁴⁴ or during the acute phase of a myocardial infarction,⁴⁵ improves heart rate variability with a proportional increase in the HF vagal component. It is interesting that those evidence-based agents with proven records of cardioprotection seem to possess either antiadrenergic activity (ACE inhibitors) or vagomimetic properties (Digoxin). With regard to the latter, it is curious that Digoxin appears to be the only inotropic agent that does not shorten survival in heart failure patients.⁴⁶ Is it because of its unique vagomimetic properties?

In short, a reasonable case can be made that shifting autonomic balance toward vagal dominance offers potential benefits to patients at high risk for ischemic-induced malignant arrhythmias. Therefore, a reasonable and testable hypothesis states that vagal afferent stimulation in humans provides clinical cardioprotection without hemodynamic compromise.

THE CLINICAL CASE FOR VAGAL AFFERENT STIMULATION IN HUMANS

In a series of controlled clinical experiments, our group observed that tonic electrical stimulation of vagal afferent fibers elicits dramatic and reproducibly sustained shifts in the heart rate power spectrum toward enhanced vagal modulation.^{47–51} This phenomenon occurs without percep-

tible changes in mean heart rate, blood pressure, or respiratory frequency.

Our first series involved a group of young patients (age 21–47 years) with intractable partial seizures who underwent implantation of an electronic vagal stimulator (Cyberonics Model 100, Cyberonics Inc., Webster, TX, USA). As part of this assembly helical electrodes are applied to the left cervical vagus, a nerve that comprises more than 80% afferent fibers. The electrodes are connected subcutaneously to a battery-driven stimulator. By switching the stimulus intensity from low (2 Hz, 0.1 mA, and 130 ms pulses) to high (30 Hz, 1 mA, and 500 ms pulses) we observed a significant increase (>70%) in the amplitude of the HF (vagal) component of the heart rate autospectrum.⁴⁷ This effect was reproducible whenever we switched the stimulator between ON and OFF positions. Moreover, the stimulation-induced vagal modulation was not only sustained over a 24-hour period but replicated a year later in the same patients.⁴⁸

We then moved on to a second series of experiments where, to gain access to vagal afferent fibers, we took advantage of the richly innervated distal esophagus. Access to these fibers was achieved with a customized 12-French manometric catheter fitted with a stainless steel electrode at the tip.⁴⁹ After advancing the catheter to 5 cm above the gastroesophageal junction we applied different modalities of vagal afferent electrical stimulations. These tests were carried out in more than 50 healthy volunteer subjects as well as patients with both gastroesophageal disorders and those with angina-like chest pain in the absence of coronary artery disease.^{49–51}

Again, as with the implantable cervical vagal stimulator, esophageal electrical stimulation caused reproducible shifts in the heart rate power spectrum toward vagal dominance.⁴⁹ No significant change in heart rate or respiratory frequency was observed across a 10-fold range in either frequency⁵⁰ or amplitude⁵¹ of stimulation. To be sure that vagal afferents were being stimulated we observed characteristic and reproducible patterns of cerebral-evoked potentials elicited with each stimulation sequence.⁵¹ Of special interest was the observation that despite a wide range of either applied frequencies (0.1–1.0 Hz) or amplitudes (2.5–20 mA), no change in the amplitude of the HF spectral power was observed once the shift to vagal dominance occurred. Nor were there significant changes in either heart rate or respiratory frequency.

Of special interest was the following observation. While the amplitude of cerebral-evoked potential increased proportional to the intensity of vagal afferent stimulation (a linear effect), the phasic signal from the brain, represented by the heart rate autospectra, remained unchanged once the initial shift to vagal dominance occurred.⁵¹ This nonlinear phenomenon implies a process that is likely occurring at a subcortical level since the initial shift in heart rate variability began before viscerosensory perception or a change in cerebral-evoked potentials occurred.

Hence, by engaging vagal afferent fibers in humans there is the possibility that one can exploit the benefits of central cardioinhibition without adversely affecting heart rate, respiration, or hemodynamics.

CONCLUSION

As a novel approach to cardioprotection in high-risk patients, vagal afferent stimulation is worthy of a dialogue. This targeted neurostimulatory effect appears to operate through central processing of enhanced cardioinhibition without the adverse effects of pharmacologic therapy. Moreover, by engaging the CNS to help modulate vagal efferent activity, it is conceivable that vagally induced protectiveness can be achieved without clinically significant alterations in heart rate or hemodynamics. Access to vagal afferent fibers for electrical stimulation is preferable to direct vagal efferent stimulation.

Before implanting any electrodes around the left cervical vagus one would want to be sure that neuroelectrical stimulation will be tolerable, safe, and effective. Herein, proper selection of responders may be achieved by first accessing and stimulating esophageal vagal afferents.

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