CHAPTER

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Vagus Nerve Stimulation

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OUTLINE

INTRODUCTION

Vagus nerve stimulation (VNS) delivered via the implantable Neurocybernetic Prosthesis (NCP) from Cyberonics, Inc. (Houston, TX) is gaining increasing popularity and credibility as a treatment option for patients with intractable epilepsy. It has also emerged as a novel adjunct in the management of patients with refractory depression and potentially other disorders. Clinical experience with VNS began in 1988 with the first human implantation of the NCP system. Since then, more than 40 000 patients worldwide have received VNS therapy, and >100 000 patient-years of experience have accrued (Cyberonics, data on file).

The NCP device delivers intermittent electrical stimulation to the left cervical vagus nerve trunk, which secondarily transmits rostral impulses to exert widespread effects on neuronal excitability throughout the central nervous system. In previous publications, we have comprehensively reviewed the theoretical rationale, practical background, and clinical application of VNS (Amar *et al.*, 1998; Amar, Heck *et al.*, 1999; Amar, DeGiorgio *et al.*, 1999; Amar *et al.*, 2001, 2004) as well as the operative procedure for inserting the NCP device (Amar *et al.*, 1998; Amar *et al.*, 2000; DeGiorgio *et al.*, 2001). This chapter summarizes the relevant considerations pertaining to VNS and reviews pragmatic issues such as patient selection and surgical technique.

NCP DEVICE COMPONENTS

Figure 50.1 depicts a schematic representation of VNS therapy. A pulse generator inserted in the subcutaneous tissues of the upper left chest delivers intermittent electrical stimulation to the cervical vagus nerve trunk via a bifurcated helical lead.

FIGURE 50.1 Schematic representation of VNS therapy. A pulse generator inserted in the subcutaneous tissues of the upper left chest delivers intermittent electrical stimulation to the cervical vagus nerve trunk via a bifurcated helical lead
(Reproduced with permission from Cyberonics, Inc.)

FIGURE 50.2 NCP pulse generator and lead
(Reproduced with permission from Cyberonics, Inc.)

In addition to the pulse generator (Figure 50.2) and implantable lead (Figure 50.3), the NCP system includes a number of peripheral components, such as a telemetry wand that interrogates and programs the pulse generator noninvasively (Figure 50.4). This programming wand is powered by batteries and is interfaced with a Dell Axim handheld that runs a menu-based software package furnished by Cyberonics. The system also includes a hand-held magnet that patients may carry with them in order to alter the character of stimulation that the generator delivers.

The NCP pulse generator has approximately the same size and shape as a cardiac pacemaker. It contains an epoxy resin header with a receptacle that accepts the connector pin extending from the bifurcated lead (Figure 50.2). The generator is powered by a single lithium battery encased in a hermetically sealed titanium module. The projected battery life of the generator varies with the stimulus parameters but can be as long as 6–10 years under normal conditions. Once it has expired, the generator can be replaced with the patient under local anesthesia during a simple outpatient procedure.

The generator contains an internal antenna that receives radiofrequency signals emitted from the telemetry wand and transfers them to a microprocessor that regulates the electrical output of the pulse generator. The generator delivers a charge-balanced waveform

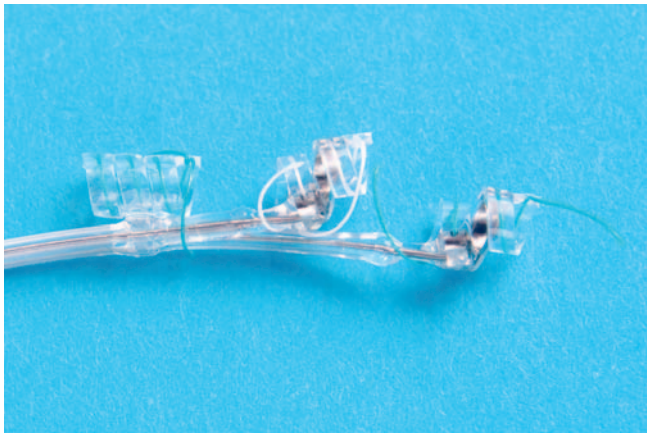

FIGURE 50.3 NCP Helical lead array
(Reproduced with permission from Cyberonics, Inc.)

characterized by five programmable parameters: output current, signal frequency, pulse width, signal-ON time, and signal-OFF time. These variables are titrated empirically in the outpatient setting, according to individual patient tolerance and seizure frequency. Altering the parameters of stimulation will have various consequences on VNS efficacy, side effects, and battery life. In clinical application, the most common parameters are 0.25–2.0 mA current (titrated to effect and tolerance),

FIGURE 50.4 NCP programming wand interfaced to Dell Axim Handheld
(Reproduced with permission from Cyberonics, Inc.)

30 Hz frequency, 500 μs pulse width, and 30-second ON/5-minute OFF duty cycle.

The generator has two accessories. One is a hairpin-shaped resistor that is used during preliminary electrodiagnostic testing prior to implantation, in order to test the internal impedance of the generator. The other is a hexagonal torque wrench that is used to tighten the set screws that secure the lead connector pins to the epoxy resin header of the generator.

While the generator is still contained within its package, it can be interrogated by the telemetry wand. The generator must pass this system check before it is opened onto the sterile field. The failure rate of the generator is extremely low, but it is recommended that a backup generator be available in the operating room at all times.

The bipolar lead is insulated by a silicone elastomer, and can thus be safely implanted in patients with latex allergies. One end of the lead contains a connector pin that inserts directly into the generator, while the opposite end contains an electrode array consisting of three discrete helical coils that wrap around the vagus nerve. The middle and distal coils represent the positive and negative electrodes, respectively, while the most proximal one serves as an integral anchoring tether that prevents excessive force from being transmitted to the electrodes when the patient turns his/her neck. The leads come in two sizes, measured by the internal diameter of each helix. Although the majority of patients can be fitted with the 2 mm coil, it is desirable to have the 3 mm one available in the operating room as well.

Each electrode helix contains three loops (Figure 50.3). Embedded inside the middle turn is a platinum ribbon coil that is welded to the lead wire. This shape permits the platinum ribbon to maintain optimum mechanical contact with the nerve. Suture tails extending from either end of the helix permit manipulation of the coils without injuring these platinum contacts. The electrode is intended to fit snugly around the nerve while avoiding compression, thus allowing the electrode to move with the nerve and minimizing abrasion from relative movement of the nerve against the electrode. Damage to the nerve is greatly reduced by the self-sizing, open helical design of the NCP electrode array, which permits body fluid interchange with the nerve. Thus, compared with cuff electrodes, mechanical trauma and ischemia to the nerve are minimized. Histological examination of the vagus nerve following VNS has revealed no axonal loss, demyelination, lymphocytic infiltration, or other evidence of permanent damage resulting from electrical stimulation (Amar *et al.*, 1998). Other observations have confirmed the safety of chronic nerve stimulation when the duty cycle (the fraction of time the nerve undergoes stimulation) is less than 50%.

The hand-held magnet performs several functions. When briefly passed across the chest pocket where the generator resides, it manually triggers a train of stimulation superimposed upon the baseline output. Such on-demand stimulation can be initiated by the patient or a companion at the onset of an aura, in an effort to diminish or even abort an impending seizure. The parameters of this magnet-induced stimulation may differ from those of the prescheduled activation. Alternatively, if the device appears to be malfunctioning or if the patient wishes to terminate all stimulation for any other reason, the system can be indefinitely inactivated by applying the magnet over the generator site continuously. Finally, patients are instructed to test the function of their device periodically by performing magnet-induced activation and verifying that stimulation occurs. Most patients can perceive the stimulation as a slight tingling sensation in the throat.

THEORETICAL BASIS OF VNS

As with many other anticonvulsant therapies, information about the neural mechanisms underlying VNS lags behind the appreciation of its clinical efficacy. The exact means by which VNS modulates seizure activity and its locus of action in the brain remain uncertain (Amar *et al.*, 1998).

The suggestion that afferent stimulation may modulate seizure activity dates back at least 2000 years to the teachings of Pelops, the master of Galen. He described a technique using ligatures applied to the limb in which partial seizures began as a means of

aborting the progression of a focal seizure or preventing its generalization. Subsequent studies have confirmed that stimulation of cutaneous afferent fibers and other sensory pathways, including direct stimulation of the cervical vagus nerve, can affect electroencephalogram (EEG) synchronization and sleep cycles. Because highly synchronized patterns are characteristic of electrographic seizures, these studies of EEG rhythmicity form the neuroanatomic and neurophysiologic foundations for the hypothesis that appropriately timed stimulation of the vagus nerve might prevent or abort paroxysmal epileptiform activity.

Although the vagus nerve is typically regarded for its efferent projections that innervate the striated muscle of the larynx and provide parasympathetic control of the heart, lungs, and gastrointestinal tract, over 80% of its fibers are special visceral and general somatic afferents leading towards the brain (Rutecki, 1990). While it was initially proposed that VNS works by recruiting afferent C-fibers and Aδ-fibers, this contention has been recently challenged by observations that VNS retains its antiepileptic effects even after selective destruction of these small unmyelinated fibers by capsaicin treatment (Krahl *et al.*, 2001).

Vagal afferent fibers originate from receptors in the viscera and terminate in diffuse areas of the central nervous system, many of which are potential sites of epileptogenesis. These include the cerebellum, diencephalon, amygdala, hippocampus, insular cortex, and multiple brain stem centers. Some of these projections relay through the nucleus tractus solitarius, while others form direct, monosynaptic connections with their targets. Although it remains unclear which of these pathways underlie the mechanism of VNS action, the locus coeruleus and raphe nucleus appear to be key intermediaries, since bilateral chemical lesions of these centers abolish the seizure-suppressing effects of VNS therapy in animal models (Krahl *et al.*, 1998).

These results imply that norepinephrine and serotonin, which are diffusely released by the locus coeruleus and raphe nucleus, respectively, may mediate the anticonvulsant actions of VNS. Indeed, these two neurotransmitters are known to modulate seizure threshold in some parts of the brain by inducing interneurons to release gamma-amino butyric acid (GABA), leading to widespread inhibition of neuronal excitability throughout the brain. However, the levels of GABA and serotonin metabolites in the cerebrospinal fluid of patients undergoing VNS appear to be inversely correlated with the efficacy of treatment, and the neurotransmitter systems that mediate the antiepileptic actions of VNS remain uncertain (Amar *et al.*, 1998).

At the stimulation parameters typically used for human application, VNS has no effect on background electroencephalography (EEG) rhythms. Vagal stimulation induces evoked responses from regions as disparate as the cerebral cortex, hippocampus, brain stem, thalamus, and cerebellum, and many authors have proposed that its antiepileptic actions relate to effects on the brain stem reticular activating system, which then projects to these forebrain structures (Amar *et al.*, 1999). However, positron emission tomography (PET) experiments measuring regional cerebral blood flow (rCBF) in response to VNS reveal changes confined to more circumscribed regions, such as the ipsilateral anterior thalamus and cingulate gyrus, contralateral thalamus and ipsilateral cerebellum, or bilateral activation of the hypothalami and insular cortices (Amar *et al.*, 1998; Amar, Heck *et al.*, 1999). The reasons for this disparity in activated rCBF patterns from study to study are not immediately apparent, but may relate to differences in stimulation parameters, individual patient variation, and other factors (Amar *et al.*, 1998). Inconsistencies between PET studies acquired during the acute versus long-term phases of VNS may reflect chronic adaptation to central processing, which attenuates responses to individual trains of VNS. Furthermore, PET studies have been confounded by multiple methodological limitations, such as seizures occurring during PET acquisition, the effects of prior cranial surgery, etc. (Amar *et al.*, 1998). In any case, the central consequences of VNS on rCBF are not as diffuse as might be expected were its effects mediated through the brain stem reticular substance (Amar, Heck *et al.*, 1999).

Right- versus left-sided vagal stimulation is equally effective in controlling seizures in animal models, and bilateral stimulation produces no measurably greater effect than unilateral stimulation (Amar *et al.*, 1998). Using techniques such as EEG and immunolabeling against *fos*, a nuclear protein expressed under conditions of high neuronal activity, these studies suggest that unilateral afferent vagal impulses generate bilaterally symmetric responses in the cerebral cortex and subcortical structures (Amar *et al.*, 1998).

In contrast, vagal efferent innervation appears asymmetric. In some species the right vagus nerve innervates the sinoatrial node while the left one preferentially supplies the atrioventricular node (Amar *et al.*, 1998). Canine studies have shown that stimulation of the right vagus nerve produces greater cardiac slowing than similar stimulation of the left vagus. For these reasons, the NCP VNS system is generally inserted on the left side, although anecdotal experience with right-sided VNS in humans has been well tolerated. Some animal studies have shown that cardiac and respiratory function are adversely affected by VNS while others have not, depending on the species used, the

stimulation parameters applied, and other variables (Amar *et al.*, 1998). Such side effects do not occur in humans because stimulation can be performed distant from the site at which the cardiac branches originate from the cervical vagus trunk (Amar *et al.*, 2000; DeGiorgio *et al.*, 2001).

CLINICAL UTILITY OF VNS

Since 1988, more than 1000 patients have participated in seven corporate-sponsored clinical trials throughout 26 countries, and greater than 3000 patient-years of data have accrued. These studies confirm the long-term safety, efficacy, feasibility, and tolerability of VNS, as well as the durability of the NCP device (Amar *et al.*, 1998; Amar, DeGiorgio *et al.*, 1999; Morris and Mueller, 1999). VNS gained approval for the treatment of medically refractory epilepsy by the US Food and Drug Administration (FDA) in 1997. Post-marketing experience validates the earlier clinical trials, and in 1999, the Therapeutics and Technology subcommittee of the American Association of Neurology declared VNS "safe and effective," based on a preponderance of class I evidence (Fisher and Handforth, 1999). Although VNS requires a large initial investment due to the price of the device itself as well as its surgical insertion, cost–benefit analysis suggests that the expense of VNS is recovered within two years of follow-up (Boon *et al.*, 1999).

When interpreting the results of VNS studies, it is important to understand the rationale behind the outcome measures used to substantiate efficacy in clinical trials of antiepileptic therapies. The most intuitive parameter is the percent reduction in seizure frequency, expressed as the mean for the entire cohort of patients. The response to VNS is not normally distributed, however. Usually, the histogram depicting response rates is skewed to the left, reflecting the disproportionate influence of the few patients who derive no benefit from therapy. Thus, a more valid summary statistic of central tendency for this non-parametric data is the median reduction in baseline seizure frequency.

Patients who enter clinical trials of new antiepileptic therapies such as VNS generally have the most intractable form of the disease. Because these patients are often pharmaco-resistant, they are not expected to become completely seizure-free by the addition of a new investigational agent. Furthermore, many patients are predicted to fail completely. Therefore, the primary outcome measure of most antiepileptic medication trials has been the 50% responder rate (the proportion of patients who achieve a 50% or greater reduction in seizure frequency). Although complete eradication of seizure activity always remains the goal of therapy, even 50% reductions can dramatically improve the quality of patients' lives.

In addition to seizure control, quality of life also depends on the side effects and toxicity of the treatment being rendered. Improvements in cognitive function and mood not related to seizure frequency *per se* are also reflected in these latter indices.

Recently, a meta-analysis was performed of the 454 patients enrolled in one of five controlled, multicenter clinical trials (two double blind and three open-label studies) conducted in the USA (Morris and Mueller, 1999). For the study population as a whole, the median reduction in seizure frequency was 35% at 1 year, 43% at 2 years, and 44% at 3 years. These results were obtained using a "last visit carried forward" analysis, which minimizes selection bias by extrapolating data from non-responders who exit the trial and thus tends to underestimate the efficacy among responders. For patients persisting in the trial (declining N analysis), sustained efficacy was even greater. An important observation is that the response to VNS is maintained during prolonged stimulation, and unlike the case with chronic medication therapy, seizure control actually improves with time.

The response of individual patients to VNS varies widely. While 1–2% of subjects enjoy complete seizure cessation, others derive no benefit. The remainder experience intermediate results. In the collective study experience, the proportion of patients who sustained a 50% reduction in baseline seizure frequency was approximately 23% at 3 months (Morris and Mueller, 1999). Although this figure is similar to the initial results of many new drug trials, the 50% responder rate also showed substantial increases with time, reaching 43% after two years (Morris and Mueller, 1999). These improvements occurred in a highly refractory population of patients who typically had an average of 1.7 seizures per day despite administration of more than two antiepileptic medications.

In spite of the well-known functions of the vagus nerve as the principal efferent component of the parasympathetic nervous system, VNS has not been shown to adversely effect any aspect of physiological function, including cardiac rhythm (as assessed by EKG and ambulatory Holter monitoring), pulmonary function, gastrointestinal motility and secretion (Schachter and Saper, 1998). It is especially significant that, unlike many antiepileptic medications, VNS therapy does not impair cognition, balance, or emotion during extensive testing. Plasma concentrations of antiepileptic medications remain unchanged.

Some adverse effects do occur with VNS, however. At three months of therapy during the acute phase

studies, hoarseness, cough, paresthesiae, and other symptoms were common, occurring in up to half of patients. These effects were rated as mild or moderate 99% of the time (Schachter and Saper, 1998). They tend to occur concomitant with stimulus delivery and not throughout the day, unlike the side effects of antiepileptic medications. Furthermore, the side effects of VNS are generally transient, and their long-term incidence is much lower. The most common complaints after 1 year of treatment were hoarseness (28%) and paresthesiae (12%) (Morris and Mueller, 1999). At 2 years they were hoarseness (19.8%) and headache (4.5%), and after 3 years shortness of breath (3.2%) was the principal side effect (Morris and Mueller, 1999). Surgical complications are rare but include infection requiring explantation (1.1%), transient vocal cord injury (<1%), and temporary lower facial paresis (<1%) (Bruce, unpublished data, 1998). Device failures are also uncommon.

More serious adverse events are rare. Although some deaths have occurred among the 454 study patients receiving VNS, none was definitely attributed to VNS therapy itself (Morris and Mueller, 1999). In fact, some studies suggest that the incidence of sudden unexplained death in epilepsy patients (SUDEP) is actually lower after treatment with VNS (Annegers *et al.*, 1998).

Patient satisfaction with VNS therapy is generally high. One way to quantify this parameter is to measure the percentage of patients who continue their therapy after completing the acute phase of a clinical trial. Continuation rates in the collective study experience were 97%, 85%, and 72% after 1, 2, and 3 years of therapy, respectively (Morris and Mueller, 1999). A related measure of patient satisfaction is the percentage of patients who opt to undergo replacement of the generator after the battery has expired. With a previous model of the NCP device, battery expiration typically occurred 4–5 years after initiating therapy, and about 75% of patients elected to change it at that time (Morris and Mueller, 1999). Long-term continuation rates reflect the unique profile of safety, efficacy, and tolerability that VNS provides.

An additional measure of patient satisfaction is assessment of overall quality of life (QOL). In randomized controlled trials, improvements in QOL were independently documented by the patient, the blinded physician, and the patient's companion using a visual analog scale (Schachter and Saper, 1998; Morris and Mueller, 1999).

Presently, VNS is only approved by the FDA "as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures which are refractory to antiepileptic medications." However, the NCP device has been successfully used in infants and youths. Subgroup analysis of the children and adolescents treated in one of the five multicenter trials suggests that they derived substantial benefit from VNS, achieving median reductions in seizure frequency and 50% responder rates at least as favorable as those in adults. Subsequently, small uncontrolled trials exclusively studying pediatric patients have been reported. The results of these latter studies appear even more salutary than those in the older populations (Amar *et al.*, 2001). A total of 60 pediatric patients were treated as part of the five prospective VNS studies conducted prior to FDA approval (Murphy, 1999). Children 12–18 years old were included in the double-blinded, controlled trials, while patients as young as 3½ years old were studied in the open-label compassionate-use protocol. After 3 months of stimulation, the median reduction in seizure frequency among these 60 patients was 23%. Using a last visit carried forward analysis, this figure improved to 31% at 6 months, 37% at 12 months, and 44% at 18 months. At 12 months, the 50% responder rate was 29%. These results are similar to those achieved by adults in the same trials. Analysis of seizures by type failed to identify any classification that was more responsive to VNS than others. Stratification into symptomatic versus idiopathic epilepsy was likewise unrevealing, since children with both types appeared to benefit from VNS in some cases. Adverse events were also similar to those in adults, and none of them necessitated termination of therapy (Murphy *et al.*, 1998; Murphy, 1999). Serious complications included aspiration pneumonia and necrosis of the skin overlying the generator site, each occurring in one child.

Similarly, VNS has been successfully applied for the off-label treatment of patients suffering from generalized-onset seizures, such as those with Lennox Gastaut syndrome (Amar *et al.*, 2001). Even the most refractory patient populations, such as those with persistent seizures after failed cranial surgery, derive significant benefit from VNS (Amar *et al.*, 2004).

In clinical practice, VNS appears to offer several advantages over pharmacotherapy and other surgical modalities. VNS avoids cerebral toxicity and the attendant impairments of cognition, emotion, and coordination that often complicate antiepileptic medication. The pre-programmed, computer-controlled characteristic of the NCP system permits complete and involuntary treatment compliance. VNS is potentially reversible, unlike cerebral surgery. Unlike the case with many medications, the effectiveness of VNS is maintained during prolonged therapy and, in fact, overall seizure frequency diminishes with time; furthermore, there are no adverse drug interactions. The improved quality of life and cognitive function perceived by patients during

VNS trials is a testimony to this unique combination of efficacy and favorable side effect profile. In addition, the ability to initiate stimulation during an aura restores an element of sovereignty to patients' lives, which are severely disrupted by the unpredictability of epilepsy. Thus, VNS is both a preventive and abortive therapy.

PATIENT SELECTION

Epilepsy affects up to 1% of the general population and is the second most common neurological disorder overall. Despite recent advances in our understanding of the molecular and cellular basis of epilepsy and the development of several new medications directed against these mechanisms, satisfactory seizure control remains elusive in 30–40% of patients. In the USA alone, there are at least 300 000 people with medically refractory seizures of partial onset. Although there is disagreement as to which of these patients should undergo cerebral surgery, it is estimated that only 30 000 to 100 000 patients are appropriate candidates for temporal lobectomy, focal cortical resection, callosotomy, hemispherectomy, subpial transection, and other extant procedures (Amar *et al.*, 1998).

The selection criteria for insertion of the NCP system remain in evolution and reflect current governmental standards as well as institutional biases and general guidelines from prior clinical trials. As noted, the "off-label" use of VNS to treat children less than 12 or those with primarily generalized epilepsy has been rewarding. Patients with both idiopathic epilepsy and seizures of structural etiology are considered appropriate candidates.

The definition of medical intractability varies from center to center. Standards from previous studies commonly required a frequency of at least six seizures per month and a seizure-free interval of no longer than 2–3 weeks despite therapy with multiple medications. However, seizure frequency, seizure type, severity of attacks, drug toxicity, and overall impact on quality of life must all be considered before a patient is deemed refractory to pharmacotherapy.

As noted above, the response to VNS is highly variable, and previous clinical trials have failed to characterize the demographic factors that predict a favorable outcome. Furthermore, VNS is rarely curative. Although reductions in seizure frequency can dramatically improve patients' quality of life, residual seizures may still preclude them from driving a car, maintaining employment, or other basic functions. Therefore, we do not consider the NCP device an alternative to conventional methods of epilepsy surgery that offer a higher likelihood of seizure cessation, and we generally reserve VNS for patients in whom such operations are not indicated. These include those patients whose seizure focus is bilateral, not associated with a structural abnormality, or cannot be completely resected due to overlap with functional cortex.

For obvious reasons, the NCP system cannot be inserted in patients who have undergone a prior left cervical vagotomy. Furthermore, the safety of VNS has not been tested in several conditions in which impairment of vagus nerve function might produce deleterious effects. Thus, relative contraindications include progressive neurologic or systemic diseases, pregnancy, cardiac arrhythmia, asthma, chronic obstructive pulmonary disease, active peptic ulcer disease, and insulin-dependent diabetes mellitus.

ALTERNATIVE USES OF VNS

In the course of studying VNS for the treatment of epilepsy, a number of serendipitous effects have been observed. Many patients report an improvement in mood, cognition, and well-being not related to seizure control per se (Amar *et al.*, 1998; Schacter and Saper, 1998; Morris and Mueller, 1999). Stimulation of the vagus nerve has been shown to enhance retention in verbal learning tasks, confirming the hypothesis that vagus nerve activation modulates memory formation similarly to arousal. In addition, VNS has been shown to exert an antinociceptive effect in rats.

As a result of these fortuities, VNS has been proposed as a possible treatment of a number of diverse neurologic conditions. One of the potential applications that has received much notoriety is depression. Several lines of evidence support this practice (George *et al.*, 2000). First is the clinical observation of substantial improvements in mood during VNS trials for epilepsy that were not attributable to seizure control alone. Second, neuroanatomic studies of vagal afferent connections suggest that the NTS and locus coeruleus project to the amygdala, stria terminalis, and other limbic structures involved in mood regulation (Rutecki *et al.*, 1990). In VNS trials for epilepsy, for instance, PET studies have shown decreased blood flow to the hippocampus, amygdala, and cingulate gyrus reminiscent of the effects of selective serotonin reuptake inhibitors and other antidepressant drugs (George *et al.*, 2000). In addition, many anticonvulsant medications have mood-stabilizing effects and are useful treatments for the depressive phase of bipolar affective disorder (George *et al.*, 2000). Conversely, electroconvulsive therapy – the most effective antidepressant therapy currently available – has potent anticonvulsant effects. Furthermore, VNS alters

the CNS concentrations of norepinephrine, serotonin, glutamate, and other monoamine neurotransmitters implicated in the pathogenesis of major depression. Finally, it is well established that depressed patients have autonomic system dysfunction that is mediated by the vagus nerve. If depressed patients have abnormalities in brain regions that control the vagus nerve from the top down, then perhaps stimulating the vagus nerve might engage this dysfunctional circuit from the bottom up (George *et al.*, 2000).

A corporate-sponsored, nonrandomized clinical trial of VNS for depression was recently conducted (Rush *et al.*, 2000). In this open-label pilot study, 30 patients with treatment-resistant depression were enrolled. All had failed at least two pharmacological trials, and more than half had failed ECT as well. Following a baseline period with stable medication regimens, patients underwent insertion of the NCP device. A 2-week single-blind recovery period was followed by a 10-week period of active stimulation, using parameters similar to those employed for epilepsy. Functional status was assessed by several scales, with response defined by a 50% or greater reduction in baseline scores.

For both the 28-item Hamilton Depression Rating Scale and the Clinical Global Impressions-Improvement index, the response rate was 40%. For the Montgomery-Asberg Depression Rating Scale the response rate was 50%. Seventeen percent of patients had complete remission. Symptomatic responses and functional improvements have been sustained during follow-up as long as 9 months (Rush *et al.*, 2000).

The promising results of the pilot study have been replicated in larger, randomized acute phase trials (Rush *et al.*, 2005). Based on these and other studies, the NCP device gained FDA approval in July 2005 "for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments."

Other hints suggest that VNS may have utility for additional neuropsychiatric illnesses. For instance, several theories of anxiety purport faulty or erratic interpretation of peripheral information that flows into the CNS (George *et al.*, 2000). By affecting the flux of this information, VNS might have therapeutic potential in treating anxiety disorders. Similarly, the vagus nerve is known to transmit signals pertaining to hunger, satiety, and pain. For those reasons, potential applications for obesity, addiction, and pain syndromes seem plausible.

The effects of VNS on feeding behavior were investigated in a canine model (Reddy, unpublished observations, 1999). Six dogs underwent bilateral VNS at parameters similar to those used for epilepsy. Feeding times, amount consumed, and weight were serially monitored and compared with baseline. In response to VNS, feeding behavior changed following a variable period of latency. Both the rate of consumption and the amount consumed decreased, leading to weight loss. When stimulation was suspended, eating returned to baseline in 3–5 days, but resuming the stimulation reproduced the initial dietary changes. A phase I clinical trial of the effects of VNS on obesity is currently in progress.

In rodent models, VNS has been shown to enhance long-term potentiation, and human studies suggest a favorable impact on recognition memory (Clark *et al.*, 1999). Based on these observations, a pilot study for the treatment of Alzheimer's disease been conducted (Merrill *et al.*, 2006). In this trial of 17 patient, 7 (42%) and 12 (70%) demonstrated improved or improved Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Mini-Mental State Examination (MMSE) scores, respectively, after 1 year of stimulation. Furthermore, there was a median reduction of cerebrospinal fluid tau protein, a marker of Alzheimer's disease severity, by 4.8% ($p = 0.057$) after 1 year.

Moreover, the NTS sends fibers to the dorsal raphe and other areas of the reticular formation known to control levels of consciousness (Rutecki, 1990). Thus, VNS has been considered as potential treatment for disorders of sleep or alertness such as narcolepsy and coma. VNS is also a possible treatment for additional conditions such as movement disorders, migraine, and others. Preliminary results in patients suffering from both epilepsy and autism suggest that VNS may exert beneficial effects in treatment of the latter condition alone (Berta *et al.*, 2005).

Finally, the NCP device permits the delivery of VNS at different amplitudes, frequencies, pulse widths, and duty cycles (Amar *et al.*, 1998). At present, these settings are titrated empirically according to desired effect and tolerability. Varying these parameters in different combinations will likely affect different regions of the brain, thereby influencing distinct pathologic conditions. As more becomes known about the physiology of afferent autonomic stimulation, the utility of VNS is likely to broaden.

OPERATIVE PROCEDURE: GENERAL CONSIDERATIONS

Insertion of the NCP device takes less than two hours and is typically performed under general anesthesia, thus minimizing the possibility that an intraoperative

seizure might compromise the surgery. However, regional cervical blocks have also been used in awake patients. While it can be performed as an outpatient procedure, it may be desirable to observe patients overnight for vocal cord dysfunction, dysphagia, respiratory compromise, or seizures induced by anesthesia, even though these complications are rare.

Prophylactic antibiotics are administered preoperatively and maintained for 24 hours postoperatively.

The implantation procedure is conceptually straightforward. The first step involves creation of a chest pocket that accommodates the pulse generator. Next, through a separate incision, the carotid sheath is opened, the internal jugular vein mobilized, and the vagus nerve trunk isolated. The lead is tunneled within a subcutaneous tract between the two incisions. The helical electrodes are applied to the vagus nerve, and the lead connector pins are attached to the generator. After additional electrodiagnostic testing, the lead and generator are secured to adjacent tissue, and the wounds are closed in standard, multilayer fashion. Others have described access to both the cervical and chest regions through a single supraclavicular incision (Patil *et al.*, 2001).

The operating room should be organized to ease the surgeon's access and to minimize traffic within the area. Following endotracheal intubation, we rotate the table 90 degrees clockwise from the anesthesia setup, which thus lies alongside the patient's right foot. This permits the surgeon to stand at the patient's left while the surgeon's assistant stands at the patient's right. The scrub technician is positioned at the patient's head, affording ready access to each surgeon on either side. The electrophysiology staff remain behind the assistant's back but within reach of the scrub technician, in order to conduct pre-implant diagnostic testing once the generator has been placed within the sterile field. Finally, prior to insertion of the first VNS system, team rehearsals should be conducted with all members of the surgical staff within the venue of the operating suite in order to review the room organization and reduce traffic within the area. These precautions may minimize the risk of hardware infection during the actual procedure.

The importance of the surgeon's preoperative preparation cannot be overemphasized. Planning for placement of the VNS system requires thorough anatomic understanding of the relevant neural, vascular, and muscular components of the anterior cervical triangle in order to minimize hazard to the ansa cervicalis, recurrent laryngeal nerve, tributaries to the internal jugular vein, and other structures. A full understanding of the anatomy of the superior and inferior cardiac branches will also reduce the rare occurrence of intraoperative bradycardia during the lead test.

In addition to anatomic review, electrode model drills with practice devices supplied by the manufacturer help familiarize the surgeon with the technique and strategy of helix placement. The surgeon is also advised to review the VNS physician's manual and surgical implantation video provided by the manufacturer prior to performing the procedure.

OPERATIVE PROCEDURE: RELEVANT ANATOMY

Several branches of the vagus nerve arise cephalad to the midcervical trunk, where the VNS electrodes are applied (DeGiorgio *et al.*, 2001). These include projections to the pharynx and carotid sinus, as well as superior and inferior cervical cardiac branches leading to the cardiac plexus. As indicated above, both the right and left vagus nerves carry cardiac efferent fibers, but anatomical studies in dogs suggest that those on the right side have a greater projection to the SA node of the heart, while those on the left side preferentially innervate the AV node (Rutecki *et al.*, 1990). For this reason, the NCP system is generally inserted on the left side. Nevertheless, stimulation of the left vagus nerve may rarely cause bradycardia or asystole, even at FDA approved settings.

As mentioned, the NCP device is generally applied to the midcervical portion of the vagus nerve trunk, distal to the origin of the superior and inferior cervical cardiac branches; this may represent another reason why the incidence of bradycardia is low. Nonetheless, the diameter, appearance, and location of the cardiac branches may approximate those of the nerve trunk itself, and care must be taken to avoid mistaking the two. If the cardiac branches are stimulated directly, small currents as low as 0.8 mA may produce significant bradycardia (Asconape *et al.*, 1999).

The superior laryngeal nerve arises rostral to the carotid bifurcation before descending towards the larynx, and high currents applied to the midcervical vagus nerve trunk may recruit these fibers, leading to tightness or pain in the pharynx or larynx. The recurrent laryngeal nerve travels with the main trunk and branches caudally at the level of the aortic arch before ascending in the tracheo-esophageal groove. As a result, hoarseness is a common occurrence during periods of stimulation or after VNS implantation.

In addition to branches of the vagus nerve trunk, several other nerves in the vicinity of the carotid sheath risk hazard from the implantation procedure itself or from subsequent stimulation. The hypoglossal nerve arises cephalad to the midcervical region,

making unilateral tongue weakness an infrequent complication of VNS implantation. The phrenic nerve lies deep to a fascial plane beneath the carotid sheath, and hemiparalysis of the diaphragm has been reported with stimulation at high output currents, though not as an operative complication.

The sympathetic trunk lies deep and medial to the common carotid artery. It gives off fibers that ascend with the internal carotid artery (ICA) towards the intracranial contents. We are aware of one case of Horner's syndrome following insertion of the VNS device, due either to manipulation of the sympathetic plexus itself or to traction on the sympathetic fibers around the ICA.

Weakness to the muscles of the lower face may result from injury to branches of the facial nerve, which ramify through the caudal aspect of the parotid gland. In general, hypoglossal and facial nerve injury are more common sequelae of carotid endarterectomy incisions, which tend to be higher than those used for placement of the VNS device.

OPERATIVE PROCEDURE IN DETAIL

The following section draws upon Amar *et al.* (2000) and DeGiorgio *et al.* (2001). The patient is positioned supine with a shoulder roll beneath the scapulae in order to provide mild neck extension. This facilitates passage of the tunneling tool that connects the two incisions. The head is rotated 30–45 degrees towards the right, bringing the left sternocleidomastoid muscle into prominence.

Many options exist for placement of the skin incisions. Often, a 5 cm transverse chest incision is made approximately 8 cm below the clavicle, centered above the nipple. The underlying fat is dissected to the level of the pectoralis fascia, and a subcutaneous pocket is fashioned superiorly. Although others have suggested a deltopectoral incision with inferior dissection to create the pocket, we believe that the scar tissue formed beneath the pectoral incision helps prevent caudal migration of the generator. Recently, we have been employing a lateral incision along the anterior fold of the axilla, which affords better cosmetic results, especially among women. Implantation of the device beneath the pectoralis muscle has also been described (Bauman *et al.*, 2006).

Next, a 5 cm longitudinal incision is made along the anterior border of the sternocleidomastoid muscle, centered over its midpoint. Generally, this incision is a little lower than that for an endarterectomy. Alternatively, a transverse skin incision at C5/6, similar to the approach for an anterior cervical discectomy, can be made. For the inexperienced surgeon, the longitudinal incision permits a wider exposure, which facilitates electrode placement through this aperture.

The platysma muscle is divided vertically, and the investing layer of deep cervical fascia is opened along the anterior border of the sternocleidomastoid, allowing it to be mobilized laterally. Following palpation of the carotid pulse, the neurovascular bundle is identified and sharply incised to reveal its contents. Self-retaining retractors with blunt blades expedite this stage of the procedure. Care is taken to limit the exposure between the omohyoid muscle and the common facial vein complex, thus minimizing potential hazard to adjacent neurovascular structures.

Within the carotid sheath at the level of the thyroid cartilage, the vagus nerve is generally encountered deep and medial to the internal jugular vein, encased in firm areolar tissue lateral to the common carotid artery. Great variability exists in the relative position of these structures, however, and the strategy by which the nerve is isolated from the remainder of the neurovascular bundle must account for such individual diversity.

We attempt to minimize direct manipulation of the nerve itself. Instead, we prefer to mobilize the vessels away from the nerve. Dissection generally commences with isolation and retraction of the internal jugular vein using vessel loops.

Next, the nerve trunk is identified and dissected with the aid of the operating microscope or surgical loupes. At least 3–4 cm of the nerve must be completely freed from its surrounding tissues. At this stage, we have found that the insertion of a blue background plastic sheet between the nerve and the underlying vessels greatly facilitates the subsequent steps of the procedure. The technique of mobilizing the vessels away from the nerve usually preserves the vasa nervosum. This nuance may reduce the incidence of postoperative complications such as hoarseness.

A tunneling tool is then used to create a subcutaneous tract between the two incisions. The tool is directed from the cervical to pectoral sites, in order to minimize potential injury to the vascular structures of the neck.

Depending on the relative size of the exposed nerve, either a small or large helical electrode is then selected for insertion. The lead connector pin is passed through the tunnel and emerges from the chest incision, while the helical electrodes remain exposed in the cervical region. Before applying the electrodes, the lead wire should be directed parallel and lateral to the nerve, with the coils occupying the gap between them.

Each coil is applied by grasping the suture tail at either end and stretching the coil until its convolutions are eliminated. The central turn of this unfurled coil is applied either obliquely or perpendicularly across

or beneath the vagus trunk and wrapped around the surface of the nerve. The coil is then redirected parallel to the nerve as the remainder of its loops are applied proximal and distal to this midpoint. The memory within the elongated coil will cause it to reassume its helical configuration and conform to the nerve snugly. Either the positive or negative terminal may be applied first, but the anchoring tether is generally applied last.

While all these maneuvers are taking place, additional electrodiagnostic testing of the generator is simultaneously carried out between the neurology team and the scrub technician. With the hairpin resistor inserted into the receptacles for the lead connector pins, the telemetry wand interrogates the device from within a sterile sheath to measure its internal impedance. Once the generator passes this pre-implant diagnostic test, it is ready for insertion.

The lead connector pin is connected to the pulse generator and secured to its receptacle with set screws, using the hexagonal torque wrench. It is important to completely insert the hex wrench into its socket in the epoxy header, in order to decompress the backpressure that builds up as the connector pins enter the receptacles. This step is essential in order to form a good contact between the lead and the generator. If the connector pin fails to make such contact, the generator may attempt to overcome the resulting increased impedance by augmenting the output current, leading to intermittent symptoms of overstimulation.

Additional electrodiagnostic examination is then performed in order to appraise the coupling of all connections and to verify the integrity of the overall system. Then, a 1-minute lead test is performed at a frequency of 20 Hz and a pulse width of 500 μs. The current should start at 0.25 mA and then ramp up in small increments to 1 mA. During this test stimulation, the response of the patient's vital signs and electrocardiogram are monitored. Rarely, profound bradycardia will result, necessitating the use of atropine. The incidence of this event is thought to be about 1 in 1000. If it occurs, attention should be directed to the lead to assure that the electrodes encircle the vagus nerve trunk itself rather than one of its cardiac branches. Following the test stimulation, the generator is restored to its inactive status until 1 to 2 weeks postoperatively. This waiting period allows for resolution of postoperative edema and proper fixation of the electrode to the nerve.

The redundant portion of the lead between the generator and electrode is secured to several areas of the cervical fascia with Silastic tie-downs. The objective is to form superficial and deep restraint configurations that help prevent excessive traction from being transmitted to the electrodes during repetitive neck motion. First, a U-shaped strain relief bend is made inferior to the anchoring tether, and the distal lead is secured to the fascia of the carotid sheath. Next, a strain relief loop is established by securing the lead to the superficial cervical fascia between the sternocleidomastoid and platysma muscles. Care is taken not to sew the lead directly to the muscle.

Finally, the generator is retracted into the subcutaneous pocket and secured to the pectoralis fascia with O-Prolene or similar nonabsorbable suture, using the suture hole contained within the epoxy resin header. Any excess lead is positioned in a separate pocket at the side of the generator. To prevent abrasion of the lead, however, it should not be placed behind the pulse generator. Wound closure then proceeds in standard multilayer fashion, using a subcuticular stitch for the skin. The cosmetic results are generally very good.

LEAD REMOVAL OR REVISION

In some circumstances it may become necessary to remove and/or replace the electrodes that encircle the vagus nerve trunk. Although fibrosis and adhesions may develop in the vicinity of the vagus nerve, Espinosa and coworkers (1999) have demonstrated that the spiral electrodes may be safely removed from the nerve, even years after they were implanted. The extent of scarring does not appear related to the duration of implant.

SURGICAL COMPLICATION AVOIDANCE AND MANAGEMENT

In the meta-analysis mentioned above, the most commonly observed surgical complication was infection. The site of the infection was either at the generator in the chest or near the leads in the neck. The overall infection rate was 2.86%, but more than half of these patients were successfully treated with antibiotic therapy alone, while only about 1.1% required explantation of the device. The causative organisms have not been reported. In many cases, the device has been replaced successfully after removal for infection.

Transient vocal cord paralysis is the second most common surgical complication of VNS implantation. The incidence of this event in the collective study experience was only 0.7%. However, since video stroboscopy and formal swallowing assessments are rarely performed after surgery, it is possible that more cases went undetected, and the true prevalence of vocal cord paresis is poorly known. Fortunately, most reported

cases resolve clinically. Vocal cord dysfunction should be minimized by careful manipulation of the vagus nerve, with preservation of its rete vascular supply and avoidance of excessive traction on the nerve.

Temporary lower facial hypesthesia or paralysis occurred in another 0.7% of patients in the meta-analysis. As stated above, excessively high surgical incisions could have been a cause.

To our knowledge, only one case of Horner's syndrome has occurred. This complication is more commonly reported after carotid endarterectomy and may be due to injury or manipulation of the sympathetic plexus immediately below the carotid sheath, or from traction on the sympathetic fibers on the internal carotid.

Lead breakage occurred commonly with earlier versions of the NCP system but has only rarely been described since device modification. Data from the manufacturer indicate that there have been a total of six lead breaks in the first 5000 implants since FDA approval (lead breakage rate = 0.12%) (DeGiorgio, *et al.*, 2001). Suturing directly to the lead body was a possible cause in one extremely early case, and generator movement that caused excessive forces on the lead electrode may have been the cause in two others (in both cases the generator was placed in breast tissue in women and the suture loop in the generator may not have been used). In another case, no strain relief loop was used.

In the first 10000 implantation procedures, only nine cases of intraoperative bradycardia or asystole have been reported, accounting for an incidence less than 0.1%. All events occurred during the lead test. Asconape and coworkers (1999) have analyzed the factors that potentially contribute to this event and the means of their prevention. As mentioned, the superior or inferior cervical cardiac branches might be mistaken for the vagus trunk itself, and correct positioning of the electrodes on the intended nerve must be verified. Proper placement of the skin incision, centered over the midcervical portion of the nerve, will also help avert this complication. Current spread to the cardiac nerves can be minimized by measures that insulate them from the midcervical vagus trunk during the lead test, such as placement of a plastic dam beneath the nerve trunk and removal of pooled blood or saline from the vicinity. Finally, the current should be ramped up in small increments during the lead test, starting with 0.25 mA.

Variants of the surgical procedure described above have been described for certain high-risk populations. For instance, patients with cognitive delay are prone to wound tampering, leading to breakdown of the incision and secondary infection. In such patients, placement of the pulse generator between the scapulae may reduce the frequency of this event. In one study of cognitively delayed children, no infections occurred in the nine who underwent interscapular pulse generator placement, in contrast to two of 14 (14%) who required device externalization after infection of their subclavicular wound (Lee *et al.*, 2002).

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