Abstract—Emerging clinical application of electrical stimulation in three systems is reviewed. In the bladder, stimulation of sacral posterior roots reduces reflex incontinence and significantly improves bladder capacity. With the combination of anterior and posterior root stimulation, bladder control can be achieved without the need for rhizotomy. Preliminary research demonstrates that bladder contractions may also be generated by stimulation of the urethral sensory branch of the pudendal nerve, even after acute spinal cord transection, while inhibition of the bladder and control of urge incontinence can be achieved by stimulation of the whole pudendal nerve. Spinal cord stimulation can modulate the activity of the intrinsic cardiac nervous system involved in the regulation of regional cardiac function and significantly reduce the pain associated with angina pectoris. Finally in the area of upper airway disorders, functional electrical stimulation has great potential for increasing life support as well as for quality of life in chronic ailments, particularly obstructive sleep apnea and dysphagia.

Key words: angina, bladder, functional electrical stimulation, incontinence, neural prostheses, neural stimulation, neuro-modulation, spinal cord injury, upper airway.

INTRODUCTION

The purpose of this paper is to review several emerging applications of electrical stimulation to restore function after neurological impairment (1). Control of three systems will be considered: the bladder, the heart, and the upper airway. The use of neural prostheses for the control of bladder function and the stimulation of the pudendal nerve for treatment of the overactive bladder will be discussed. Potential mechanisms of pain relief from angina pectoris with spinal cord stimulation will be explored. And finally, the role of electrical stimulation in treating four different upper airway disorders—obstructive sleep apnea, dysphagia, bilateral vocal fold paralysis, and laryngeal dystonia—will be considered.

CONTROLLING REFLEX INCONTINENCE IN SPINAL CORD INJURY BY NEUROMODULATION

Physiologic voiding involves bladder contraction and urethral sphincter relaxation. Both voiding and the storage of urine by the bladder require properly coordinated spinal-brainstem-spinal reflex loops (2). In spinal cord injury (SCI) these loops are damaged, resulting in the loss of voluntary sphincter control, sensation of
bladder fullness, and proper coordination of the bladder and urinary sphincters. As a consequence, bladder emptying is impaired and the result is reflex incontinence.

Reflex incontinence is primarily caused by detrusor hyperreflexia, an aberrant reflex that emerges after a period of spinal shock following SCI. It is often associated with dyssynergenic contractions of the sphincter muscles of the urethra, preventing efficient emptying of the bladder. Persons with SCI invariably have large residual bladder volumes, have recurrent urinary tract infections, and more seriously, can develop a susceptibility to renal impairment if the condition is not treated properly. Conservative treatment is usually a combination of drugs for suppressing detrusor hyperreflexia and intermittent catheterization for emptying the bladder. However, the antimuscarinic drugs used to treat incontinence often have debilitating side effects, such as loss of bowel control secondary to constipation, dry mouth, and visual disturbance. Voiding can also be very troublesome, especially for women for whom no simple collection vessels exist, and intermittent catheterization can sometimes introduce bladder infections. These problems, among others, demand that more satisfactory therapies for bladder management in SCI are developed.

In the 1970s, Brindley and his team developed an implantable stimulator to empty the bladder of paralyzed persons (3). The prosthesis uses sacral anterior root stimulation (Finetech-Brindley SARS, Finetech Medical Limited, Wellyn Garden City, UK) to activate bladder motor pathways and produce clinically effective voiding (Figure 1). For reflex incontinence and sphincter dyssynergia to be overcome in these subjects, the sacral sensory nerve roots from S2 to 4 have to be cut (sacral deafferentation). The Finetech-Brindley device has been

![Figure 1.](image)

**Figure 1.**

Finetech-Brindley Extradural Sacral Anterior Root Stimulator Implant: (a) implantable receiver (Internal Stimulator) connected by cables to electrodes placed extradurally next to sacral nerves carrying motor fibers to bladder detrusor muscle. For prevention of reflex incontinence, sacral afferent nerves from S2–4 are cut at conus level through a small laminectomy marked “X.” For emptying of bladder, a transmitter coil is aligned with implanted receiver on outside of skin and pulses are transmitted transcutaneously to activate nerves with short bursts of electrical stimulation. (b) Traces showing rises in bladder and urethral pressures generated by each burst of supramaximal stimulation at 30 pulses/s, each pulse being up to 500 µs in duration. When bladder pressure is sufficient to overcome residual urethral pressure, between bursts of stimulation, then bladder emptying occurs.
Grindley device, but without sacral deafferentation, to test the concept of SPARSI. Each of these subjects was assessed preoperatively with DPN stimulation as described above to demonstrate the efficacy of neuromodulation. Preliminary results indicated that subjects were able to achieve both suppression of reflex incontinence and clinically useful increases in bladder volume with the use of the implanted stimulator (12) (Figure 4). Interestingly, intermittent stimulation also appeared to produce good results, although the ideal interval between bursts has yet to be determined. The bladder volumes achieved with neuromodulation were equivalent to those achieved with the antimuscarinic drug oxybutinin in individual subjects. Hence, this device appears to be an effective therapy for reflex incontinence.

SPARSI does elicit good bladder contractions through anterior root stimulation but at a much higher stimulation level than is needed for neuromodulation of successfully used in many countries throughout the world (4) and is starting to be more widely used in the United States under the name of Vocare (NeuroControl Corporation, Valley View, Ohio). The implant has been shown to be very effective in increasing bladder volume, promoting complete emptying of the bladder, reducing bladder infections, and significantly improving the quality of life for many subjects. However, the need for sacral deafferentation (posterior rhizotomy) with the consequent loss of reflex erections and reflex ejaculation can deter many potential young male subjects from accepting SARS. Furthermore, the hope by some subjects of a “cure” for SCI in the future using neural regeneration and repair techniques is a further obstacle to acceptance. However, there may be an alternative solution to sacral deafferentation with the use of stimulation of these same afferent pathways to suppress reflex incontinence.

The development of a sacral posterior and anterior root stimulator implant (SPARSI) is being explored in which stimulation of the anterior roots to empty the bladder is combined with stimulation of the posterior (sensory) roots to prevent reflex incontinence with the same implant to activate the mixed roots (5).

Preliminary studies using noninvasive multipulse magnetic stimulation over the sacrum have shown that suppression of reflex incontinence can be achieved with stimulation of the mixed sacral roots (S2–4) in subjects with detrusor hyperreflexia (6). The mechanism for this “neuromodulatory” action has yet to be determined in man, but one theory, based on experimental work in animals (7), suggests that neuromodulation involves inhibitory action by pudendal afferent (sensory) nerve stimulation on pelvic nerve motor pathways to the bladder through spinal cord circuits (Figure 2) (8). Evidence in support of this theory has been obtained by stimulating pudendal afferent pathways at the level of the dorsal penile (9) (or dorsal clitoral) nerves in subjects. Dorsal penile nerve (DPN) stimulation applied through surface electrodes produces a profound and repeatable suppression of the bladder both when applied conditionally (i.e., when bladder pressure increases during detrusor hyperreflexia) or continuously (pre-emptively) in subjects with SCI (10) (Figure 3). Furthermore, in addition to decreasing reflex incontinence, DPN stimulation can produce significant increases in bladder volume (11). These effects depend essentially on stimulation and diminish when stimulation is switched off.

Recently, four subjects with a SCI have been implanted with a standard bilateral extradural Finetech—
reflex incontinence. However, simultaneous high-level stimulation of the mixed roots does cause persistent reflex sphincter contractions between the bursts for bladder contraction, and this elevates urethral pressures to a level where bladder emptying is often impaired. For this problem to be overcome, tests are now being done with
the use of a variety of techniques including selective nerve blocking (“anode block”) of sphincter motor pathways with specially shaped electrical pulses, a method previously shown to be effective in experimental models (13).

Ultimately, it is hoped that by combining neuromodulation for reflex incontinence with neurostimulation for bladder emptying in SPARSI, we can completely control the bladder without cutting any sacral sensory nerves, thereby preserving all pelvic floor reflexes in people with a SCI.

PUDENDAL NERVE STIMULATION FOR TREATMENT OF OVERACTIVE BLADDER

Overactive bladder is a new definition adapted by the International Continence Society and recently by an NIH consensus panel on terminology in urogynecology. This is a symptom-based diagnosis, including conditions such as detrusor instability, urge urinary incontinence, detrusor hyperreflexia, unstable bladder, and frequency/urgency syndrome. Traditional diagnoses, based on urodynamic findings, missed 40 to 60 percent (NOBLE Study Group, 2001, unpublished data) of affected subjects with lifestyle-altering lower urinary tract symptoms. Specifically, there are subjects with incapacitating urinary frequency and urgency, without incontinence, that are undiagnosed and untreated based on traditional diagnoses.

Approximately 33 million Americans, or 16.6 percent of the adult population have overactive bladder (NOBLE Study Group 2001, unpublished data). Overactive bladder is a serious problem that significantly impacts a person’s quality of life. Affected individuals tend to have significant sexual dysfunction, poor self-esteem, and limited physical activities and social interactions (14–15). Some subjects do respond to behavioral therapy, such as bladder and pelvic floor retraining, timed voiding, and biofeedback, but the standard therapy continues to be pharmacological treatment. Antimuscarinic drugs such as tolteradine and oxybutinin are the mainstays of treatment. The problem with these drugs is compliance because of the undesirable side effects (16).

For those who fail traditional therapy, there is now sacral neuromodulation. Sacral root stimulation has been demonstrated to be an effective treatment for urge urinary incontinence, frequency/urgency syndrome and nonobstructive urinary retention. However, the implant procedure usually requires general anesthesia and two separate incisions for the stimulating lead and pulse generator. Reoperation rates remain high and are usually for lead migration or pain (17).

Electrical stimulation of the pudendal nerve has been demonstrated to inhibit detrusor activity, and chronic electrical stimulation may provide effective treatment for overactive bladder disorders (18). The hurdle to date has been the technical challenge of placing and maintaining an electrode near the pudendal nerve in humans; however, recent development of the BION has made chronic implantation feasible.

The BION is a small, self-contained microstimulator that can be injected directly adjacent to the pudendal nerve. The ischial spine is an excellent marker for the pudendal nerve as it reenters the pelvis through Alcock’s canal. This is a very consistent anatomical landmark in both men and women. Also, the implanted electrode is protected in this area by both the sacral tuberous and sacrospinous ligaments. Stimulation in this area activates afferent innervation over up to three sacral segments (Figure 5). Efferent stimulation also provides direct activation of the external urethral sphincter, the external anal sphincter, and the levator ani muscles, which may be of some benefit in bladder control. The external components of this neural prosthesis include a coil that is worn around the subject’s hips and a controller that is worn around the shoulder or waist (Figure 6).

Figure 5.
Posterior view of BION implant site adjacent to the pudendal nerve. BION can be injected directly adjacent to pudendal nerve. Afferent pudendal pathways are shown with black dots and efferent pudendal pathways are shown with white dots.
The optimum insertion location is 1.5 cm medial to the ischial tuberosity with the use of a vaginal finger to guide the implant toward the ischial spine where electrical stimulation of the pudendal nerve may be confirmed.

Subjects with overactive bladder symptoms refractory to other therapies were considered potential candidates for chronic pudendal nerve stimulation. The group evaluated included women 18 to 80 years old with no infection, malignancy, pelvic pain, or pregnancy. All subjects underwent a complete history and physical examination, urine analysis, urine culture, and a screening electrodiagnostic evaluation. The average age of the subjects enrolled in the study was 61 years, average weight was 159 lb, and the average length of disease was 5.7 years. Each of them had tried at least two medications and had at least one previous urogynecological surgery.

A percutaneous stimulation test (PST) was developed and proved to be a very effective way to assess acute changes in bladder volumes while stimulating the pudendal nerve. A baseline cystometrogram (CMG) was obtained followed by percutaneous pudendal nerve stimulation for 10 minutes with a repeat CMG. Two stimulation modes were tested, continuous and intermittent. With both types of stimulation, all parameters of bladder function were remarkably improved. The order in which the stimulation was provided was varied and did not appear to make a difference (Table 1).

The first implant was done on August 29, 2000. The BION was implanted under local anesthesia with intravenous sedation. Proper placement was verified by palpation and EMG activity. An intermittent stimulation mode of 5 seconds on and 5 seconds off was used. Subjects returned 5 to 7 days later for activation, to distinguish between postoperative pain and potential stimulation pain. Subjects were followed up at 15, 30, and 45 days after activation. At each follow-up visit, they underwent another cystometrogram and brought in a 72-hour voiding diary. The results indicated a favorable response to maximum cystometric capacity throughout the study period. Diary entries verified improvement—incontinent episodes decreased by 65 percent, and both daytime and nighttime voids were decreased, as was pad use per day (Table 2).

In general, there were no perioperative complications with either the percutaneous study or the implant. The mean duration of stimulation was 8.6 hours per day. With a minimal amount of stimulation, normal voiding was facilitated. The feasibility of direct pudendal nerve stimulation in a minimally invasive manner has been...
established. The percutaneous stimulation test may indeed be a useful test to predict candidates for future BION implantation. A favorable response of the lower urinary tract to chronic pudendal nerve stimulation was also observed. Most importantly, the subjects were satisfied with the device and indicated that it is having a profound effect on their quality of life.

PUDENDAL URETHRAL SENSORY NERVE STIMULATION FOR BLADDER EVACUATION

Another emerging application of pudendal nerve stimulation is electrical activation of urethral sensory nerve fibers to elicit bladder contraction and voiding (19). This approach is based on the augmenting reflex, whereby fluid flow in the urethra initiates bladder contractions in the quiescent bladder and augments ongoing contractions in the active bladder (20,21). Preclinical studies in animals demonstrated that bladder contractions may be generated by electrical stimulation of the urethral sensory branch of the pudendal nerve (19,22), and that the urethrobadder reflex was preserved following acute spinal transection (19–22). The excitatory urethrobadder reflex was found to be strongly state-dependent (19,23). When the bladder is at low volumes, electrical stimulation of the urethral sensory branch does not cause excitation of the bladder but evokes an increase in urethral sphincter activity. When the bladder is at higher volumes, electrical stimulation of the urethral sensory branch of the pudendal nerve leads to excitation of the bladder (24) and micturition-like increases in bladder pressure (19,22), and prolonged stimulation leads to long-term augmentation of the urethrobadder reflex (25). These results challenge the traditional view that coordinated voiding requires intact spinal-brainstem-spinal reflex loops (2) and suggest that the interneuronal circuitry required to elicit coordinated bladder evacuation exists within the spinal cord. This may provide a new approach to restoration of bladder evacuation following SCI.

MECHANISMS OF PAIN RELIEF FROM ANGINA WITH SPINAL CORD STIMULATION

Angina pectoris associated with ischemic heart disease is referred pain that subjects generally feel as crushing, burning, and squeezing. The pain is usually sensed in the chest although it can sometimes radiate to the left arm and left jaw (26,27). The mechanism is believed to depend on convergence of cardiac afferent information on spinothalamic tract cells that also receive cutaneous and muscle afferent input (28,29). Thus the same pathway is transmitting different information but the areas of the brain involved with nociceptive processing have “learned” to interpret the cardiac information as coming

Table 1.
Percutaneous Stimulation Test (PST) results. These data represent acute cystometrogram changes seen with percutaneous stimulation of the pudendal nerve.

<table>
<thead>
<tr>
<th>Stimulation mode</th>
<th>1st sensation (cc)</th>
<th>1st urge to void (cc)</th>
<th>1st Max cystometric capacity (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>132.4 ± 56.1</td>
<td>196.4 ± 88.3</td>
<td>325.0 ± 150.5</td>
</tr>
<tr>
<td>Continuous</td>
<td>188.0 ± 88.9</td>
<td>330.4 ± 127.6</td>
<td>501.0 ± 192.3</td>
</tr>
<tr>
<td>Intermittent</td>
<td>298.6 ± 40.4</td>
<td>377.4 ± 61.2</td>
<td>609.8 ± 167.8</td>
</tr>
<tr>
<td>Significance</td>
<td>(Kruskal-Wallis)</td>
<td><em>p = 0.009</em></td>
<td><em>p = 0.03</em></td>
</tr>
</tbody>
</table>

Table 2.
Voiding diary summary before implanting BION (baseline) and at 15, 30, and 45 days postimplant.

<table>
<thead>
<tr>
<th>Study period</th>
<th>Incontinent episodes per day</th>
<th>Daytime voids</th>
<th>Nighttime voids</th>
<th>Pads per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.5 ± 2.6</td>
<td>7.8 ± 3.0</td>
<td>1.8 ± 1.7</td>
<td>4.3 ± 4.2</td>
</tr>
<tr>
<td>Day 15</td>
<td>1.7 ± 3.0</td>
<td>4.8 ± 2.4</td>
<td>0.4 ± 0.8</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>Day 30</td>
<td>1.6 ± 2.7</td>
<td>6.0 ± 1.0</td>
<td>0.7 ± 0.5</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>Day 45</td>
<td>1.5 ± 1.5</td>
<td>6.5 ± 1.2</td>
<td>1.0 ± 1.0</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>Percent change</td>
<td>64.6 ± 44.4%</td>
<td>17.9 ± 30.9%</td>
<td>38.6 ± 43.3%</td>
<td>51.0 ± 34.8%</td>
</tr>
</tbody>
</table>
from somatic structures. Angina pectoris can be a deceptive symptom. It may present itself in subjects who have normal coronary arteries, angina may be absent in subjects whose ECG indicates significant ischemia, and this pain can be unrelated to origin because the esophagus can readily mimic angina pectoris (30).

Under normal conditions, exercise produces an increase in a value called the rate pressure product, an increase in heart rate and blood pressure producing a greater demand by the heart for oxygen. However, in ischemic heart disease, coronary blood flow is impaired. In these subjects, exercise increases oxygen demand that results in an imbalance between coronary blood flow reserve and myocardial oxygen consumption (31). The symptomatic result of ischemic heart disease under these conditions is angina pectoris. Typically, chronic stable angina can be treated with medications, such as ACE inhibitors, beta blockers, and calcium channel inhibitors (32). Other common treatments include revascularization procedures such as percutaneous transluminal angioplasty or coronary artery bypass surgery.

Unfortunately, there are subjects who have chronic refractory angina pectoris but do not get sufficient pain relief or restoration of function even from optimal medical treatment (32). These are subjects with reversible myocardial ischemia resulting from significant coronary artery disease, and they cannot be treated with additional revascularization. Between Europe and the United States, approximately 70,000 to 80,000 people have this problem and are not being treated.

Adjuvant therapies for chronic refractory angina pectoris include restoration of function using rehabilitation and angiogenesis, transpedicular anesthetics, external counter pulsation, and destructive therapies such as sympathectomy and laser ablation (33,34). Another therapy that has shown promise in relieving chronic refractory angina is neuromodulation via spinal cord stimulation (SCS). In Europe, this technique has been beneficial in approximately 80 percent of the cases (35). In addition, about 60 percent of the subjects experienced improved exercise capacity and quality of life for up to 5 years (36,37). It appears to be a safe, cost-effective, and reversible therapy, but its mechanism of action is still not understood (34). Subjects who receive SCS still experience the pain of myocardial infarction even when the stimulator is on, and thus the warning system is still intact (32,33,38,39).

The procedure for SCS to alleviate angina involves the insertion, under local anesthesia, of an electrode between the T9 and T11 vertebrae (35). The electrode is then moved epidurally up to the T1 to T2 level and placed just to the left of midline. The stimulation is turned on and tests are run to confirm that paresthesia evoked by activation of the stimulator is sensed in the somatic regions where the subject experienced angina pectoris. A typical subject regimen would be stimulation three times a day for 1 hour in addition to stimulation during an angina attack (35). The subject can activate or deactivate the stimulation by either using a magnet or subject programmer. If exercise is anticipated, the stimulus intensity can be increased prior to the onset of exercise.

The challenge is to determine the underlying mechanisms that produce the anginal pain relief experienced with SCS. Spinal cord stimulation influences the processing of information within the central nervous system (40,41). Furthermore, SCS increases peripheral blood flow (42–47). Recent studies have shown that the intrinsic cardiac nervous system of the heart serves as a final common neuronal regulator of cardiac function (48). Because the intrinsic nervous system is interposed between the information processing of the central nervous system and cardiac function, it was proposed that SCS might modulate the processing of the final common neuronal regulator (49).

Recent studies have shown that the intrinsic cardiac nervous system strongly influences heart function. The intrinsic cardiac nervous system is generally located in seven to eight areas of the heart that contain fat pads with aggregates of cardiac neurons and neural interconnections embedded within them that modulate cardiac function (48). These intrinsic cardiac neurons receive a stream of inputs from the neurons of the spinal cord to regulate regional cardiac function with each beat (49–51). Changes in the activity of the intrinsic nervous system can alter ventricular regional blood flow (52). Transient ischemic episodes of ventricular regions can markedly increase the activity of the intrinsic cardiac neurons (53). It is also important to note that chemical activation of intrinsic cardiac neurons can lead to restricted cardiac dysrhythmias (54). An important feature of the neural organization is that it is a hierarchy of control from higher centers down through the spinal cord and into the intrinsic nervous system to determine how the heart is modulated (Figure 7).

Experiments were performed in animal models to determine if the intrinsic cardiac nervous system could be modulated with SCS (Figure 8) (49). Results indicated that both transient coronary occlusion and subsequent
reperfusion increase intrinsic cardiac neuronal activity. Spinal cord stimulation is able to suppress this activity, even during transient myocardial ischemia (Figure 9). An interesting observation was that during the 15 minutes of stimulation, the intrinsic cardiac activity was suppressed; however, this suppression continued for another 15 to 30 minutes after the stimulation was turned off (55). In some cases these activities remained suppressed for 2 to 3 hours. Thus, there is a marked ability to change that nervous system such that it becomes less responsive once SCS has been applied.

In summary, SCS of the upper thoracic segments suppresses the function of the intrinsic cardiac nervous

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**Figure 7.**
Schematic diagram of hierarchical levels of integration important in neural control of heart. Hierarchy comprises descending projections from spinal cord and medulla and, as a consequence, Higher Centers from brainstem and cortex. These descending projections continuously influence Intrinsic Cardiac Nervous System in ganglionated plexi via input and modulation that occurs in Intrathoracic Extracardiac Ganglia (IEG). Dashed lines and stippled boxes represent afferent feedback originating from heart. Black lines with arrows illustrate direct and successive synaptic relays from medulla and spinal cord, within this autonomic neuronal hierarchy. Please note that black arrows within Intrinsic Cardiac Nervous System and IEG represent afferent and efferent connections, and Local Circuit Neurons (LCN).

Hierarchy of peripheral autonomic nested feedback loops functions in an interdependent manner to regulate regional cardiac function on a beat-to-beat basis. (NODOSE, ganglion for vagal afferent fibers; DRG, Dorsal Root Ganglia for sympathetic afferent fibers; Symp, Sympathetic; Parasymp, Parasympathetic; β1, Beta-adrenergic receptors; M2, Muscarinic receptors).

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**Figure 8.**
Schematic diagram of experimental setup for examining effects of spinal cord stimulation on activity generated by intrinsic cardiac neurons in right atrial ganglionated plexus: (A) Placement of a quadropole electrode on dorsal surface of spinal cord (C, Cervical; T, Thoracic). Electrode was stimulated with a stimulator. (B) Penetration of a microelectrode in right atrial ganglionated plexus (gray ellipse, intrinsic cardiac nervous system) of heart. (C) Recordings of intrinsic nerve activity (ICN) on chart and tape recorders, an oscilloscope (CRO), and computer. Cardiovascular recordings were also stored on recorders and computer (ECG, electrocardiogram; BP, blood pressure; LV IMP, left ventricular intramyocardial pressure).

**Figure 9.**
Responses of averaged activity (impulses per minute, imp/min) generated by intrinsic cardiac neurons (right atrial ganglionated plexus) during occlusion of left coronary artery and spinal cord stimulation. Hatched horizontal bar represents period of coronary artery occlusion (CAO), and stippled bar is period of SCS. First bar is control intrinsic activity and last bar is recovery of activity. These results show that SCS significantly reduces activity generated by intrinsic cardiac neurons even during CAO. *Represents data that were significantly different from control values ($P < 0.05$).
system that serves as the final neural regulator of cardiac function, even in the face of a myocardial ischemic challenge. Thus, SCS may alter the function of the intrinsic cardiac nervous system to protect the heart from some of the detrimental consequences resulting from myocardial ischemia that lead to angina pectoris.

UPPER AIRWAY APPLICATIONS FOR ELECTRICAL STIMULATION

Another emerging area of clinical application of electrical stimulation is the treatment of upper airway disorders, and four disorders are discussed. The first is obstructive sleep apnea, which is a prevalent disorder that can have severe negative consequences on an individual’s quality of life and even be life threatening, for example when it causes people to fall asleep behind the wheel of a car. The second is dysphagia; swallowing disorders are also prevalent, life threatening, and induce significant health care costs. Third is bilateral vocal fold paralysis, a rare but life-threatening problem. Finally, laryngeal dystonia will be discussed, a condition that results in a disabling speech disorder.

The current treatment options available for all four disorders are less than ideal. Sleep apnea is treated with tissue excision, which is painful and permanent and not always beneficial. Dysphagia subjects with chronic aspiration have to be put on nothing by mouth and enteric feeding with permanent gastrostomy PEG, which requires nursing care. Bilateral vocal fold subjects have tracheostomy, which does provide a temporary airway, but prohibits subjects from showering and swimming, and increases their risk of infection. In the case of laryngeal dystonia, botulinum toxin can provide temporary benefit in adductor spasmodic dystonia, but is not effective in abductor spasmodic dystonia.

Obstructive Sleep Apnea

In obstructive sleep apnea, the tongue muscle relaxes during sleep and the tongue falls into the pharyngeal area, narrowing the hypopharynx. With inspiration, airflow through this area produces a negative pressure, sucking the pharynx closed to produce a further obstruction in the hypopharynx. There has already been some attention given to using hypoglossal nerve stimulation to dilate the hypopharynx during sleep (56). However, there have been problems with the nerve cuff associated with this technique, probably because the tongue has many strong movements in the floor of the mouth during swallowing and chewing that could injure the nerve.

Recently, genioglossus stimulation with the use of percutaneous electrode insertion has been considered. In this approach, a 30-Hz, 3-mA pulse is delivered for 1 second to result in the epiglottis being pulled forward to prevent the collapse of the pharynx. In preliminary studies done with control subjects, this stimulation produced rather dramatic opening of the hypopharynx. Particularly impressive was the rapid rate of opening that occurs and that this opening remains sustained during stimulation. Therefore, it is believed that genioglossus stimulation does have potential, particularly if a selected region of the genioglossus is targeted. This approach carries less risk of hypoglossal nerve injury that could cause swallowing problems. The next phase is subject evaluation.

Dysphagia

It has been shown in previous clinical studies that the usual cause of aspiration in dysphagia is a problem with laryngeal elevation. Reduced extent of elevation and delayed onset of elevation often can allow the bolus of food to enter the airway before the onset of swallowing. Lack of opening of the upper esophageal sphincter also results in the food remaining in the pharynx. Reduced speed and extent of laryngeal elevation or closure are the most prevalent in disorders such as postmedullary CVA, where the brainstem central pattern generator is thought to be involved in swallowing, and also in neurodegenerative diseases (57).

In preclinical studies that examined the potential use of neural stimulation to treat swallowing problems, control of laryngeal closure was investigated (58). A relatively noninvasive technique was used, percutaneous insertion through the thyroid cartilage, to implant an electrode directly in the thyroarytenoid muscle, which is the major muscle in the vocal fold. Results indicated that the anterior part of this muscle appeared to be most effective in closing.

To examine the effects of using this instrumentation over time, we evaluated six dogs for 4 to 8 months with implants in the two superior and the two inferior thyroarytenoid muscles. Unilateral intermittent stimulation was used, 5 seconds on and 5 seconds off, for 8 hours per day. Intermittent stimulation was chosen because the laryngeal muscles are very fast muscles; 90 percent of the fibers are type II myosin and at risk for conversion to slow fibers under continuous stimulation. Monthly evaluations comparing stimulated with nonstimulated sides
were performed. With stimulation, the velocity of movement in the larynx was improved significantly. Intermittent stimulation did not alter muscle histochemistry; there was no conversion to slow fiber type in chronically stimulated dogs. Unilateral thyroarytenoid stimulation was found to produce bilateral closure, suggesting that this muscle can be thought of as a sphincter.

Based on preclinical studies in which mylohyoid stimulation produced elevation of the larynx, a clinical study is ongoing to determine if stimulation of the mylohyoid and thyrohyoid muscles could assist in elevating the larynx in the human. Fifty percent of swallowing elevation was achieved with stimulation of just one of the muscles, and greater than 50 percent elevation could sometimes be achieved when both muscles were stimulated. It was also found that the two muscles elevate faster than either one muscle alone. This approach might be used in treating stroke subjects during early rehabilitation when they are having difficulty swallowing.

**Bilateral Vocal Fold Paralysis**

In bilateral vocal fold paralysis, the reduced opening of the folds becomes closed when airflow during inspiration produces a negative air pressure, sucking the folds closed. In recent clinical studies of chronically paralyzed subjects, stimulation of the denervated posterior cricoarytenoid muscle was able to produce opening of the vocal folds (59).

Many subjects who have vocal fold paralysis do eventually reinnervate; however, by the time they do, the muscle is often fibrotic and the joint is not flexible. FES was evaluated preclinically to determine if stimulation could be used to condition the muscle to remain healthy until reinnervation occurs. The results were very good; the movement threshold in the sectioned side of an animal that had received stimulation decreased over time and the velocity over time increased. However, in examining the animals in the final end of the year stimulation, the sectioned side still remained immobile during spontaneous breathing. Thus, this application would require chronic implant and would not be able to prevent the long-term effects of synkinesis interfering with voluntary movement.

**Laryngeal Dystonia**

The most common form of laryngeal dystonia is a spasmodic dystonia, a voice disorder that occurs in middle life, which can cause disabilities prohibiting an individual from being able to work due to an ineffective voice for communication. The most frequent type of this disorder, adductor spasmodic dysphonia, is well managed with the use of botulinum toxin; however, the more rare abductor spasmodic dysphonia is not.

Subjects with this latter condition experience a reflexive opening of the glottis, which is thought to be caused by over activity of the posterior cricoarytenoid muscle. Continued stimulation of the thyroarytenoid muscle during speech has been shown to reduce symptoms, particularly in more severe subjects (60), suggesting that there might be some role of neuromuscular stimulation for use in speech communication as well.

Application of electrical stimulation in upper airway disorders is clearly an emerging area. Speech, breathing, and swallowing are important functions with few treatment options available for persons chronically impaired by neurological disorders affecting these functions. The challenge is that the muscles in this region are very small and the muscles are used differently for speech, chewing, swallowing, and coughing. Thus ability to stimulate one specific muscle without dislodging the hardware is a technical concern that must be addressed. In addition, the head and neck area is very dense with vascularization and nerves, so surgical implant techniques are going to require skill and experience.

**CONCLUSION**

There appear to be many potential applications of electrical stimulation beyond the most familiar uses to restore upper- and lower-limb movement. Although there is a long history of electrical stimulation for restoration of bladder emptying, new applications in the area of bladder management are emerging. The primary focus of these new applications is on restoration of continence and will result in the more widespread application of this technology. Similarly, spinal cord stimulation has been applied to neuropathic pain since the late 1960s. However, new applications for control of angina pain and other aspects of cardiac function are emerging. Success in new applications will require a greater understanding of mechanisms by which spinal cord stimulation exerts its effects. Clearly, a number of applications of electrical stimulation exist for restoration of function in the upper airways. These are quite advanced and require multicenter clinical trials of safety and efficacy to move forward.
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