Spinal Cord Stimulation: Principles and Applications

22

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Introduction

The concept of electrical stimulation applied for the treatment of pain was first documented in a book published in 47 AD called the *Compositiones* by Scribonius Largus. Largus demonstrated that shock incurred by the torpedo ray induced analgesia for both gout and headaches. A substantial amount of progress has occurred since that time, providing treatment for a wide range of clinical symptoms using various electrical stimulation modalities. There are two clinical applications for electrical stimulation to nerves. The first is designed to treat motor disorders such as tremors caused by advanced Parkinson's disease. The more common use for electrical stimulation uses focused electrical treatment to neural targets resulting in analgesia. Current targets for stimulation include the spinal cord, dorsal root ganglia, and peripheral nerve tracts.

The predominant use of electrical stimulation is spinal cord stimulation (SCS), where direct electrical stimuli are applied to the spinal cord for the treatment of chronic pain. This concept is based on gate control theory by Melzack and Wall [1]. This theory dictates that the stimulation of large beta fibers closes the gate on small fiber transmission resulting in perceived analgesia.

Shortly after gate control theory was introduced, electrical stimulation for the treatment of pain progressed rapidly with the introduction of new devices and applications. In 1967 Wall and Sweet used infraorbital stimulation for the first time. Later that year, the first spinal cord stimulator was implanted by Shealy and Mortimer. One year later, in 1968, Sweet and Wepsic implanted the first peripheral nerve stimulator. The first commercial spinal cord stimulator was introduced by Medtronic in that same year. The

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standard non-rechargeable batteries were replaced by the first rechargeable battery in 2004 by Advanced Bionics which later became part of Boston Scientific.

Currently, neuromodulation has three primary manifestations: spinal cord stimulation, peripheral nerve stimulation, and intracranial stimulation of the deep brain and motor cortex. There are two major advantages to these therapies: reversibility of treatment and treatment trial prior to permanent implant. The trial of the device allows the patient to test the treatment in a more minimally invasive manner to determine efficacy. The technical goal is to obtain overlap of electrical stimulation on painful areas. The clinical goals are reduction in pain, improved function and quality of life, and reduction in the amount of analgesic pain medication. Indications for the device in the USA are failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS). Indications for the device in Europe are ischemic pain caused by peripheral vascular disease and intractable angina.

Spinal cord stimulation is a useful therapy in the treatment of a multitude of pain conditions. A literature review of SCS in FBSS patients revealed that SCS is effective in relieving the chronic intractable pain associated with the syndrome [2]. This type of neuromodulation is also reported to be effective in certain applications for discogenic pain and Reynaud's syndrome by altering sympathetic outflow, resulting in increased blood flow and decreased pain [3]. Neuromodulation is a promising treatment for long-term chronic and neuropathic pain modalities.

Physiology and Biophysics of Neuromodulation

Understanding the physiology behind SCS requires review of basic neurologic functioning at both the cellular and axonal levels. Recall that each axonal cell body in the inactive state has a negative resting potential. Upon activation of the axonal cell body, the inward sodium current increases the resting potential to the threshold potential. Once the threshold potential is reached, an action potential is initiated. This action potential propagates down the axon via salutatory conduction in myelinated axons. However, the basic transduction of the signal from the spinal cord stimulator electrode to the biological system is often poorly understood.

To better comprehend this concept, conduction of electrical signals in nonbiological systems must be understood. In nonbiological systems, electrical current is carried via a conducting medium (in this case, the conductive material in the spinal cord stimulator lead). The electrical current in the SCS lead electrode results in the flow of electrons producing an electrochemical reaction. There are two types of electrochemical reactions: galvanic and electrolytic. Galvanic cells *produce* electrical energy while electrolytic cells *consume* energy. In basic terms, the SCS is a galvanic cell while the biological system is an electrolytic cell. The SCS electrodes have non-insulated regions known as "contacts" that provide the interface between the SCS and biological tissue. This contact is programmed to be either positive (anode or oxidative contact) or negative (cathode or reductive contact). By convention, electron flow is described as moving from the positively charged anode to the negatively charged cathode. This flow of electrons creates an electrical field. It is the size and "shape" of the generated electrical field that clinicians manipulate to produce the desired clinical result with SCS systems [4].

The conduction of electrons in the SCS lead is a Faradaic reaction. A Faradaic reaction is flow of charge electrical (i.e., nonbiological) systems such as wiring. When the electrical field produced by the flow electrons in this electrical system contacts biologic tissue, the energy (galvanic reaction) is converted or transduced into a biological flow of charge. This biologic flow of charge is produced by the movement of the ions in the electrolyte cellular solution and is known as a non-Faradaic process.

For example, an electrode is placed into non-ionic water. The water molecules are electrically neutral but do have regions of charge (positive oxygen/negative hydrogen). When the negatively charged (cathode) is produced, the water molecules move to orient themselves with the positive region of the molecule facing

the negatively charged electrode contact. In an electrolyte-containing solution, the positively charged ions (sodium in the case of the axon) move toward the negatively charged electrons when an electrical field is generated. This movement of sodium creates a regional charge imbalance which, if occurring at the neuronal membrane, alters the resting membrane potential and activates an action potential. This sequence of events transduces the electrical energy of the SCS into an action potential within the sensory fibers of the dorsal columns of the spinal cord [5]. The resulting sensory activation is felt by the patient, and the sensation is described as a *paresthesia*.

This paresthesia, when overlapping the dermatome or region of neuropathic pain, competes with pathologically activated pain pathways within the dorsal horn. Through a complex signal processing and conduction, this sensation reaches the higher brain centers [6]. The dorsal horn acts as a processing station for incoming sensory information. Sensory input such as the sensation of pain and the generated paresthesias are processed simultaneously by the dorsal horn, and the representative sensory input is relayed to the cortex [7]. This process is known as signal convergence. Signal convergence within the spinal cord is utilized by SCS to create an analgesic effect [7]. In essence, the presence of a non-noxious paresthesia produced by the SCS system competes with the noxious stimulus from the pain fibers. As described in the gate control theory of pain, this non-noxious stimulus acts to dampen the painful noxious stimulus at the level of the dorsal horn.

Ohm's law governs the properties of the electrical field generated. The components of Ohm's law, voltage, current, and resistance (and the close corollary impedance), are best thought of regarding fluid dynamics. In this case, voltage is roughly analogous to the force or pressure of water, resistance to the size of the opening through which the fluid moves, and current to the volume of fluid that moves through the opening in a unit of time. Using a garden hose as an example, if the nozzle opening is made smaller (i.e., an increase in resistance) but pressure (i.e., voltage) is held constant, flow or current will decrease. Since the relationship of Ohm's law is $V = I \times R$, when voltage is held constant, an increase in resistance will result in a decrease in flow or current. The other relationships follow similarly.

This is a vital concept, since SCS systems control the (dependent) variables of voltage or current, while resistance (or its close corollary impedance) tends to be a function of the biologic system and, therefore, an independent variable. These considerations are debatable from a clinical standpoint as it is presently unclear if constant voltage or constant current SCS systems provide different clinical results.

Basics of Spinal Cord Stimulator Programming

The electrical field generated and the paresthesia elicited by the electrical field can be customized to patient preference. For example, each "pulsation" or electrical field has an amplitude (or strength of pulsation), a pulse width (how long the pulse lasts), and a frequency rate (pulses per second) (Fig. 22.1). These parameters can be

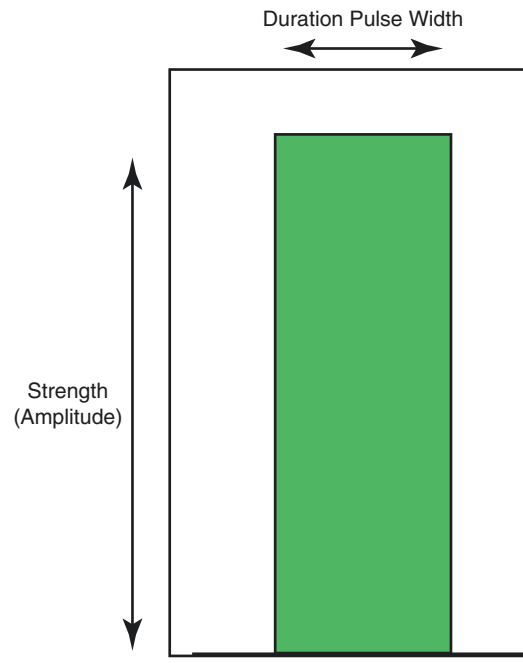

Fig. 22.1 Square pulse commonly used for spinal cord stimulation, which is dependent on amplitude and pulse width

manipulated to alter the perception of the stimulation paresthesia. When a SCS lead is in place over the target tissue, the strength of the pulse is gradually increased until the patient first detects the stimulation. This is called the *perception threshold*. The stimulation may be increased to a therapeutic value and ultimately may be increased beyond the ability of the subject to tolerate the sensation. This is referred to as the *discomfort threshold* or the amplitude (strength) at which the patient no longer tolerates the stimulation. It is important during the trial and implantation phase to carefully determine these parameters, as a subject with a very narrow ratio of perception to discomfort thresholds (i.e., narrow therapeutic range) may describe the stimulator as "shocking" them or decrease use due to dissatisfaction with the paresthesia.

The pulse or stimulation rate can be manipulated to create distinct pulses. Settings of the SCS can vary between a low rate or a merging of pulse sensations with higher frequency stimulation. Lower frequencies result in a more distinct, slower pulse, while higher frequencies result in a more continuous, smoother sensation.

Complex mathematical modeling of the impact of these parameters on SCS function has been done. Named for Jan Holsheimer, the concept of mapping out the proper lead positioning and concomitant SCS parameters for optimal effect has become known as Holsheimer mapping [8]. While they are advanced concepts, the mathematical underpinnings of SCS programming are important issues to understand when complex programming is required. Pulse width provides an illustrative example of this concept. For example, if a spinal cord stimulator lead is placed in a more lateral position within the epidural space, a longer pulse width may activate the spinal cord nerve root and cause discomfort. In this scenario, narrowing the pulse width may be beneficial.

Electrical Field

The shape of the electrical field created is dependent on the configuration of anodes and cathodes. In a simple system using one anode and cathode, charge flows as described above with very little ability to "shape" the contour of the electrical field (Fig. 22.2). Over the last 10 years, the utilization of an electrode combination referred to as a "guarded cathode" has proven useful. This configuration has anodes on either side of the negative cathode setting up an electrical barrier to the spread of the electrical field, driving the field in a targeted fashion (Fig. 22.3). This concept is important to successful trialing of SCS as the ability to "steer" current toward the target areas of pain determines the ability to produce the overlapping

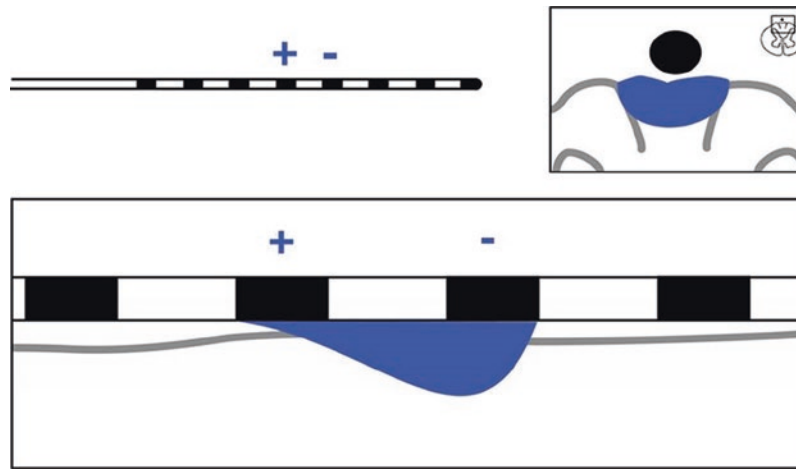

Fig. 22.2 Single anode and cathode configuration

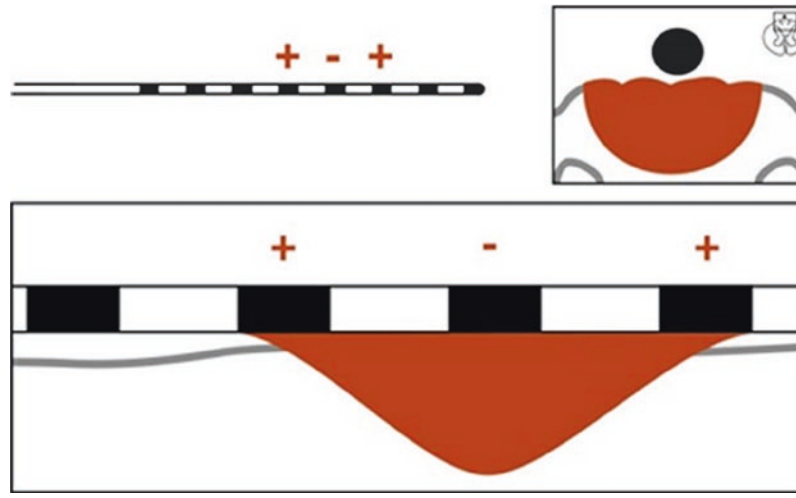

Fig. 22.3 Guarded cathode configuration

paresthesia. In the above example, the clinical usefulness of driving charge deeper into the spinal cord may be the difference between successfully capturing the desired paresthesia level and an unsuccessful trial.

Technical Aspects of Lead Placement

Preplacement Planning

Spinal cord stimulation can be utilized at all spinal levels and as such requires some preplacement planning. For example, cervical leads can be placed at the cervico-thoracic junction or via a lumbar access site with the lead maneuvered through the epidural space to the cervical target. Both approaches have merit but different applications. If one is conducting a temporary trial, then the "work" of threading leading leads from the lumbar spine for a patient who may not derive benefit may be futile [9]. Conversely, if the leads are for a permanent implant, the lumbar placement negates the need for lead extensions or extensive subcutaneous tunneling. Similarly, if leads are to be placed in the sacral space, a decision must be made whether to attempt placement in a retrograde fashion or via the sacral hiatus.

While there is wide variability among individual patients, there are some guidelines with regard to lead placement targets which may assist the clinician in preplacement planning. For instance, it is widely accepted that in the cervical spine, the C2–C5 region will encompass the shoulder to the arm/hand. Likewise many have observed that obtaining paresthesia coverage for pain in the cervical axial spine is often difficult. Pain of thoracic origin can be broadly categorized as intercostal and visceral. Intercostal paresthesia can often be obtained at or just above the thoracic level of injury in a lateral position, while visceral pain (an area of emerging application for SCS) is currently not well defined and can be highly variable when obtained at all. Paresthesia coverage of pain of lumbar origin is better described. Classic teaching states that the "target zone" for most lumbar pain has an upper limit at T8 level with neurologic mapping undertaken to find the exact location between T8 and L1 that works best for a given patient. Lumbar lead placement between L2 (termination of the spinal cord) and L5 is occasionally helpful and has many features in common with nerve root stimulation since the dorsal horn terminates at the T12–L1 level with the conus medullaris (the distal portion of the spinal cord proper at the L1–2 level). Sacral targets, though technically difficult to access, typically are relatively straightforward in their preplacement assessment in that the affected painful level is typically the optimal site for lead placement.

Physiologic Versus Anatomic Positioning

Regarding "ideal" lead placement, there is considerable variability among individual patients. Many times "ideal" lead placement based on the fluoroscopic images obtained during initial placement (Fig. 22.4) results in nontherapeutic paresthesia patterns, the second image (see Fig. 22.4) being the physiologically correct placement for that particular patient. This observation has led to the description of an anatomical midline and a physiological midline or "sweet spot" (Fig. 22.5). This jargon is describing the consistent finding that ideal anatomic position of the SCS lead under imaging (anatomic midline) often requires repositioning of the lead to less aesthetically pleasing but more desirable physiologic position to obtain paresthesia coverage of the painful area (physiologic midline). This concept suggests that dorsal column fiber position is variable among individuals, even when the spinal cord is clearly midline on MRI or CT scanning. Another aspect of this physiologic mapping that must be considered is the common observation that one patient may report paresthesia into their feet at T8 while others will experience this same sensation at T10. Further, some individuals, despite meticulous repositioning, never achieve desired paresthesia coverage of the painful area.

Anatomical Conservations

Fiber location within the spinal cord, while also variable, does have some general principles that warrant discussion. Nerve fibers of more distal structures are contained in more central locations within the spinal cord. These fibers become more superficial as they near the exit point within the spinal cord. A spinal cord homunculus analogous to the homunculus at motor cortex has been described that suggests that sacral, lumbar, and

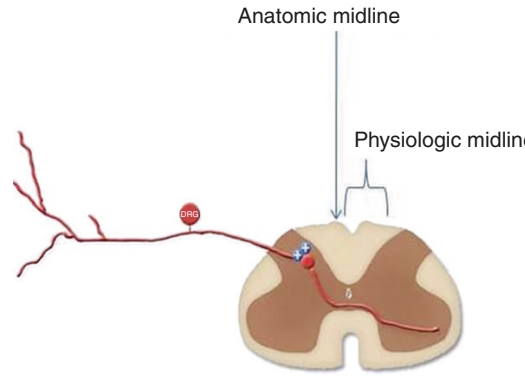

Fig. 22.5 The anatomical midline and the physiological midline or "sweet spot," terms that describe the consistent finding that ideal anatomic position of the SCS lead under imaging (anatomic midline) often requires repositioning of the lead to less aesthetically pleasing but more desirable physiologic position to obtain paresthesia coverage of the painful area (physiologic midline)

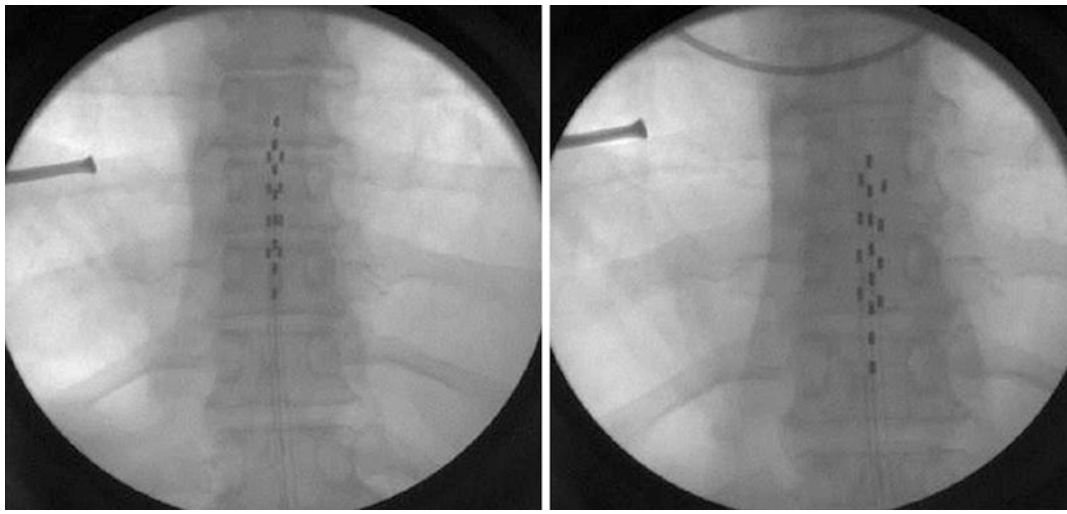

Fig. 22.4 Fluoroscopic image obtained during initial placement (*left panel*) of the "ideal" lead placement and the physiologically correct placement for this particular patient (*right panel*)

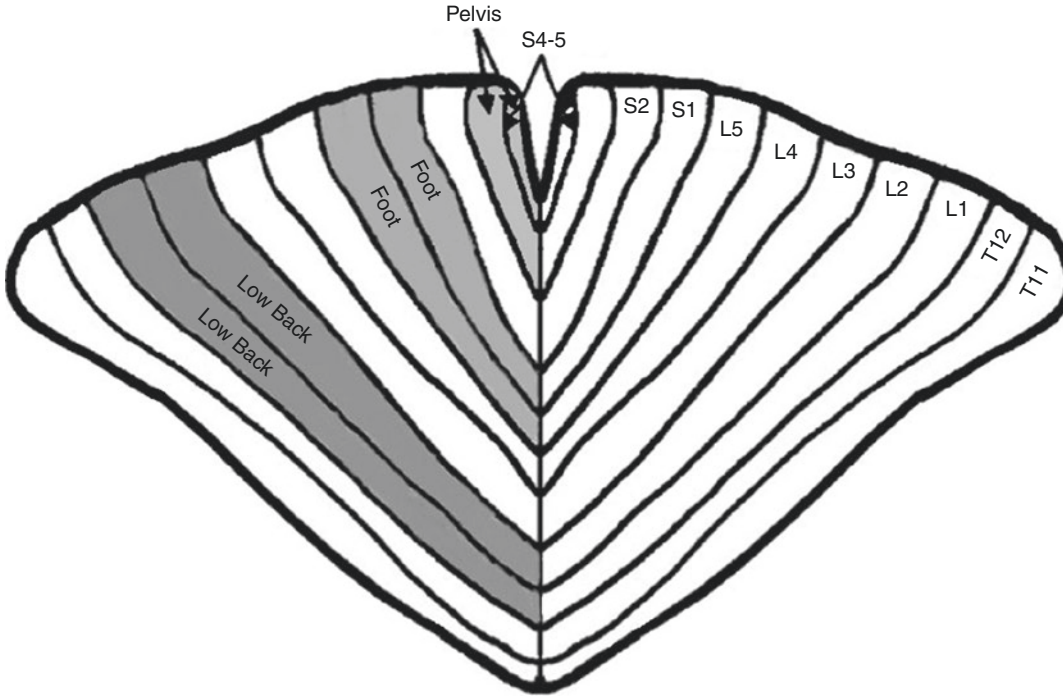

Fig. 22.6 Nerve fibers of more distal structures are contained in more central locations within the spinal cord. These fibers become more superficial as they near the exit point within the spinal cord. A spinal cord homunculus analogous to the homunculus at motor cortex has been described that suggests that sacral, lumbar, and thoracic fibers occupy fixed positions within the spinal cord ranging from medial to lateral, respectively

thoracic fibers occupy fixed positions within the spinal cord ranging from medial to lateral, respectively (Fig. 22.6). While this concept is widely taught, paresthesia mapping during trialing suggests that the concept of fiber position is of little practical value as the important lead position is the one that has practical clinical value to the patient. Also, it has been reported that nociceptors that innervate the axial spine are located at deeper levels within the spinal cord and as such require complex combinations of pulse width and amplitude to achieve penetration to these fibers [10]. With newer spinal cord stimulation modalities such as stimulation at 10,000 Hz or Burst stimulation, the anatomic position of the leads becomes more prescribed [11]. For instance, with newer waveforms, paresthesia mapping is less important; however placement in anatomic zones becomes key. For high frequency stimulation, the placement of leads in the midline in a linear array across the thoracic 9th and 10th disc interspace is prescribed as best practice. Though less prescriptive, burst spinal cord stimulation seems to have an anatomic "sweet spot" from T8 to T9 in the anatomic midline.

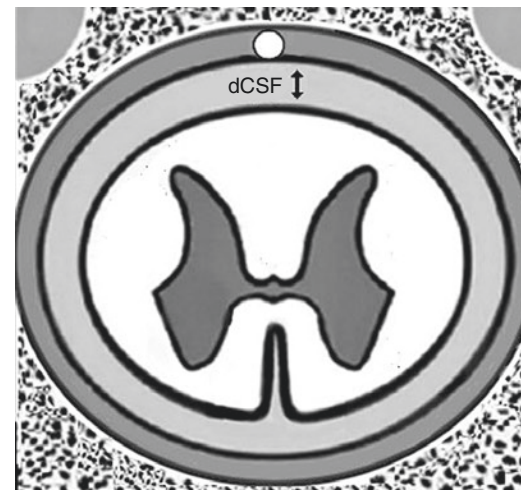

Fig. 22.7 The CSF thickness varies along the spinal column and can significantly impact stimulation

Distance between the dura and the spinal cord significantly impacts SCS. The dural cerebrospinal fluid volume varies widely along the length of the spinal cord (Fig. 22.7) and influences the dispersion of current. The CSF levels are maximal at

the T5–7 level, which fortunately from a clinical standpoint decrease in the common target zones of C4–6 and T8–L1. The CSF volume at T8–L1 is still significant enough to impact stimulation.

Technical Considerations and Trialing Techniques

Technical Considerations

The number of contacts and leads to be utilized in SCS treatment is a matter of much conjecture and little conclusive evidence. In the mid-2000s, a single or dual four-contact lead system was the state of the art. A study conducted during this period suggested that there was little advantage in adding a second lead for either radicular lower extremity or low back pain [12]. In this study, the dual lead system was associated with faster implantable pulse generator (IPG) discharge, without significant improvement in perceived pain relief. Technological advances in IPG battery life coupled with more sophisticated programming options have led to rapid adoption of eight-contact leads which when used in an 8 × 2 array result in all channels of the IPG occupied and available to be utilized [13]. A 16-contact lead has recently entered the market and is already undergoing clinical testing using a 16 × 2 array for enhanced coverage and reducing the need for lead adjustment due to lead migration. The enhanced coverage would only necessitate reprogramming as opposed to additional surgeries.

Leads configured in multiple combinations such as two leads (bipole) and three leads (tripole) have been suggested to enhance coverage of low back pain. This concept is currently under investigation. The introduction of the tripole concept allows the clinician to mimic lead contact coverage obtained with a surgical plate or "paddle" lead [14]. The broad "paddle" lead has wider contact spacing allowing coverage of a wider area within the spinal cord. There also seems to be less lead migration with the paddle lead.

Another advantage over the percutaneous lead lies in the shape of the lead itself. The cylindrical percutaneous lead "radiates" an electrical field in a 360° direction, while the surgical paddle lead directs current toward the spinal cord. It has been proposed that this arrangement directs current "deeper" into the spinal cord and may allow better axial back pain coverage. With the multiple contact percutaneous lead, the greater contact capability (8 × 1) does allow the clinician to potentially retain paresthesia coverage even if small degrees of lead migration occur [15]. It remains to be seen if the increased number of contact points is of significant benefit from a clinical perspective.

Interleaving

The programming capabilities of multiple contact points allow the programmer to utilize an advanced concept known as *interleaving* to cover multiple areas of pain. The fundamental basis of this approach utilizes the programming of the IPG to rapidly (in microseconds) switch back and forth between programs on separate portions of the lead that cover different areas of pain. For example, in an 8 × 2 configuration, lead contact 0–4 on a left-sided lead may cover low back pain, while 11–15 on the right may cover the radicular lower extremity pain. With rapid cycling between the two areas of lead contact, the patient perceives coverage of both areas. The interested reader is directed to several excellent manuscripts on this topic.

Constant Voltage Versus Constant Current

As discussed previously, all SCS systems are bound by Ohm's law in the way that they transduce the electrical signal to the biological system. If resistance (impedance in these alternating current systems) is relatively constant, and this is dependent upon the biological milieu, the only variables that can be manipulated are voltage and current. The advantages of both approaches can be theoretically debated with excellent arguments emerging for both types of systems. One study has compared constant voltage and constant current in a randomized trial, allowing the patient to

determine whether there was a preference between constant voltage and constant current systems. In this small preliminary study, patients could not reproducibly identify constant current systems from constant voltage systems, suggesting that the theoretical differences may not translate into clinically meaningful differences in therapy [16]. This fascinating topic deserves further research.

Spinal Cord Stimulation Trial Techniques

After careful preplacement planning has been accomplished, it is necessary to plan the trailing process. It is recommended that all patient candidates for SCS should undergo a pretrial psychological assessment to determine if there are unrealistic expectations, secondary gain issues, psychological issues that have not been maximally explored and treated, or other biopsychosocial factors that may impact treatment success. Once this has been done, it is necessary to discuss with the patient the trialing technique. The purpose of the trial is to temporarily allow the patient to experience the sensation of SCS without having to endure the full implantation process with the IPG. There are two types of percutaneous spinal cord stimulator trials: (1) temporary percutaneous and (2) staged percutaneous placement with permanent anchoring of the leads. Each trialing method has advantages and disadvantages. The more common temporary percutaneous method entails securing the trialed lead to the skin with suture or other easily reversible material in a fashion that is quickly and simply removed. The percutaneous placement with permanent anchoring method requires surgical incision after lead placement and anchoring identical to that which is done with permanent implantation. The anchored leads are then connected to disposable trial connectors and exteriorized via tunneling in an operative setting.

The advantages of the more common temporary percutaneous placement in comparison to permanent anchoring method are (1) easy placement and removal, (2) can be done in office procedure setting (whereas the surgical anchoring requires a traditional operating suite), (3) less post-procedure discomfort to distract the patient from the trial process, and (4) less invasive. Conversely, the percutaneous placement with permanent anchoring results in a more accurate trial to implant experience and less surgical time required for implantation of the IPG [17]. Additionally, the IPG placement can be performed under deeper sedation/general anesthesia since sensory mapping is not necessary. Occasionally, the results of the temporary trial are superior to the actual implant using the former method resulting in significant patient dissatisfaction. In the pretrial planning process, if it is suspected that spinal epidural access or lead manipulation will be difficult, it may be reasonable to do the staged trial with permanent anchoring; otherwise, most centers utilized the temporary percutaneous method.

Regardless of trialing method, it is imperative that adequate time with the therapy be given to the patient to determine efficacy. Balancing the need for time with the therapy with the risk of infection usually results in 3–5-day trial period although some clinicians advocate for at least 7 days [18]. Experience with infection rates of epidural catheters suggests that any trial up to 7–10 represents low risk from an infection standpoint. During the trial, evaluation of functional capacity, sleep hygiene, and pain reduction is key. The person who does not derive functional benefit but claims pain relief should be evaluated closely.

High-Frequency Spinal Cord Stimulation and High-Frequency Burst Stimulation

For decades traditional SCS settings have dominated the market; however, over the last 8 years, there has been promising data emerging from the increasing use of high-frequency (10 kHz) spinal cord stimulation devices (HF10) burst stimulation. These devices have similar clinical indications as the traditional SCSs and have been approved by the US Food and Drug Administration for the treatment of both back and leg pain. They operate based on the same positional and electrical current

delivery models as the traditional devices. However, contrary to the frequencies used for traditional SCS (40–120 Hz), these newer devices create currents with frequencies of 10 kHz or use burst impulses of five separated at 40 Hz with internal burst frequencies of 500 Hz or greater. While the frequencies of these devices are increased, the amplitude of the current itself is markedly decreased to levels such that they don't elicit a motor or sensory response. Therefore, in contrast to the previously described devices so highly reliant on paresthesia development to determine both proper placement and efficacy, high-frequency devices at appropriate settings do not require what can be unformatable paresthesias to generate a response.

While these devices are still in their infancy, the data are promising. A 2-year multicenter randomized control trial which included nearly two hundred patients demonstrated long-term superiority of HF10 therapy when compared to the use of traditional SCS [19]. The study examined 198 patients with chronic leg and back pain randomized into HF10 therapy or traditional SCS treatment groups and used primary and secondary end points of 3-, 12-, and 24-month intervals with respect to pain relief. What was found is that at each temporal interval, the patients demonstrated both non-inferiority and superiority of pain relief in the HF10 population [19].

In response to the significant clinical benefit of these devices, researchers have begun to explore and postulate regarding their mechanism of action. The Gate Control Theory which lead to the development of the initial SCS treatment devices does not hold water with regard to HF10 devices. The pillar of traditional paresthesia-based SCS devices is the activation of the dorsal columns and gracile nucleus to alter the interpretation pathways of pain [20]. Multiple animal studies and computer modeling have shown that HF10 therapy does not activate or even change the conduction properties of the dorsal column fibers, the gracile nucleus, or even simple peripheral mechanical stimulation responses [19, 20]. The response to the device itself is described vastly different: HF10 treatment requires hours to days to develop maximum pain relief, whereas SCS relief is apparent nearly immediately. Tiede et al. performed a multicenter prospective trial of HF10 therapy on patients who had previously tried and failed traditional SCS therapy and found 88% of the patients responded to the HF10 treatment [20]. This study further alludes to a unique mechanism of action of the HF10 treatments given its marked ability to induce relief in patients who were otherwise nonresponders to treatment.

There are multiple "working hypothesis" undergoing investigation currently as to how HF10 therapy mitigates these pain pathways: depolarization blockade, membrane integration, desynchronization, and glial-neuronal interaction [20]. The depolarization blockade theory suggests that an electrical field is created similar to the tradition model such that the neurons are further depolarized but in a local revisable manner. The membrane integration hypothesizes that the summation of the pulsatile signals creates an action potential whereas the single pulses alone would not induce a response. Both the depolarization and the membrane integration theories which mandate an altered neuronal stimulation response have data to contradict the theories. The desynchronization theory describes complex neuronal networks firing in synchrony to communicate pain and HF10's ability to desynchronize these firings. Finally, although the published data are lacking, the glial-neuronal theory describes a reformed activation of the astrocytes and microglia cells to alter the somatosensory pathways of pain [20].

Clinical Indications

While SCS has been utilized for a variety of painful axial and neurological conditions, the main indications for the therapy are as follows:

1. Failed back surgery syndrome: It has been shown that SCS has better outcomes than reoperation. These findings suggest that a trial of SCS before considering a second back surgery should be a part of the treatment algorithm.

2. Radicular pain: Pain of radicular nature in a classic dermatomal distribution in either the cervical, thoracic, or lumbar spine has a relatively strong evidence base suggesting efficacy.
3. Neuropathic pain: Perhaps the strongest indication is the intense pain of neuropathic origin. Entities such as complex regional pain syndrome types 1 and 2, post-herpetic neuralgia, and post-amputation limb pain all respond well to SCS. Of these indications, CRPS has strong clinical data to suggest efficacy.
4. Peripheral vascular disease: Such as Raynaud's phenomena, nonoperative limb ischemia, chronic angina, and Berger's disease.

While these clinical scenarios are well established as responding to SCS, there are several exciting areas of emerging application for spinal cord stimulation. Many of these applications have evidence from the case report level to suggest they may improve pain control in patient who has exhausted other possibilities. These off-label applications include:

1. Visceral/abdominal pain: There are case studies to suggest that neuromodulation can successfully be used to improve analgesia for pancreatitis and other pain of visceral origin.
2. Peripheral neuralgia: Spinal cord stimulation technology has been successfully used to treat peripheral nerve pain such as ilioinguinal/iliohypogastric neuralgia and occipital neuralgia.
3. Peripheral field nerve stimulation (PFNS): While still in the emerging stages, there is evidence of improvement with pain of myofascial and other origins that is resistant to treatment with subcutaneously placed electrodes. There have been studies published that discuss a cross-talk between the epidural and peripherally placed electrodes providing a synergistic effect for resistant peripheral pain syndromes.

Of these applications, peripheral nerve stimulation has strong data to suggest its efficacy, while visceral/abdominal applications and PFNS are still in the early stages of description.

Complications

Complications from SCS include the discomfort from implantable pulse generator (IPG), lead migration, fracture or malfunction, malfunctioning of the IPG, infection, dehiscence of wound, formation of seroma, or unwelcomed paresthesia or dysesthesias 20 [21]. A 2015 single university hospital retrospective, observational study (n = 234) saw an all complication rate of 34.6% from SCS, the majority being hardware related (Table 22.1) [20, 21]. The study saw that SCS revision and explant rate were both 23.9% (Table 22.2) [21]. An overview of complications, diagnoses, and resultant therapies is seen in Table 22.3 [22].

Table 22.1 Complications summary

	N	Complication rate (%)
All complications	81	34.6
Hardware	60	25.6
IPG discomfort or migration	26	11.1
Lead migration	20	8.5
Lead malfunction or fracture	10	4.3
IPG malfunction	4	1.7
Biologic	21	9.0
Infection	10	4.3
Unwanted paresthesia or dysesthesia	6	2.6
Dehiscence or seroma of wound	5	2.1

Adapted from Hayek et al. [21]
IPG Implantable pulse generator

Table 22.2 Revisions and explants causes

	Revisions	Explants
IPG migration or discomfort	18	8
Migration of lead	18	2
Lead malfunction or fracture	7	2
Malfunction of IPG	2	2
Infection	0	10
Required MRI	0	4
Paresthesia or dysesthesia	0	6
Dehiscence of seroma of wound	2	1
Requested by patient	0	1
Surgery requirement	0	1
Therapeutic effect that has been lost	9	23

Adapted from Hayek et al. [21]

Table 22.3 Overview of complications, resultant diagnosis, and available treatments

Symptomatic diagnosis	Complication	Treatment
Complications within neuraxis		
CT or MRI, electromyogram/nerve conduction study (emg/ncs), physical exam	Nerve injury	Steroid protocol, anticonvulsants, neurosurgery
Increased stimulation amplitude	Epidural fibrosis	Lead programming, lead revision
Physical exam, CT, or MRI	Epidural hematoma	Surgical evacuation, steroid protocol
Physical exam, CT or MRI, CBC, blood work	Epidural abscess	Surgical evacuation, IV antibiotics, ID consult
Positional headache, blurred vision, nausea	Post-dural puncture headache	IV fluids, rest, blood patch
Complications outside neuraxis		
Serosanguineous fluid in pocket	Seroma	Aspiration, if no response surgical drainage
Blood in pocket	Hematoma	Pressure and aspiration, surgical revision
Pain on palpation	Pain at generator	Lidoderm patches, injection, revision
Fever, rubor, drainage	Wound infection	Antibiotics, incision and drainage, removal
Device-related complications		
Lack of stimulation in area of pain	Unacceptable programming	Reprogramming of device, revision of leads
Inability to program, X-rays	Lead migration	Reprogramming, surgical revision
High impedance, pain at leak site	Current leak	Revision of connectors, generator, or leads
Inability to read device	Generator failure	Replacement of generator

Adapted from Deer et al. [22]

Table 22.4 Lead migration rates for SCS

Publication	*N*	Migration rate (%)	Publication type
Cameron 2004	2753	13.2	Review article
Turner 2004	830	23.1	Systematic review
North 2005	45	9	RCT
Taylor 2005	112	27	Systematic review
Kumar 2006	410	21.4	Retrospective analysis
Kumar 2008	42	14	RCT
Mekhail 2011	527	22.6	Retrospective analysis
Gazelka 2014	143	2.1	Restrospective review
De Vos 2014	40	2.5	RCT
Total	4968	Range 2.1–27	
		Mean 15.49	
		95 CI 9.21–21.77	

Adapted from Eldabe et al. [23]
RCT Randomized control trial

The most common hardware complication of SCS is lead migration. A 2015 literature review that analyzed the complications of SCS found that lead migration occurred at a mean rate of 15.49% (95% CI 9.21–21.77%) (Table 22.4) [23]. Lead migration can cause therapeutic paresthesia coverage loss; however IPG reprogramming may be all that is required to reestablish therapy. Unfortunately, most lead migrations are significant enough to warrant SCS lead revision. Factors that increase the risk of lead migration include the placement of percutaneous cylindrical leads (versus surgical paddle lead placement) and placement of leads in areas of the spine that is highly mobile, e.g., cervical spine. Other hardware complications in SCS include lead fracture and malfunction (6.37%; 95% CI 2.63–10.10%). Premature IPG battery failure is a rare hardware complication [23].

Pain related to an implanted SCS is a biological complication that has a reported mean incidence of 6.15% (95% CI 0.97–11.33%) (Table 22.5) [23]. Patients may localize pain at the IPG or lead anchor sites or at the lead extension points [23].

Wound infection is a major biological complication of SCS. The 2015 literature review reported a mean wound infection rate of 4.89% (95% CI 3.38–6.39) (Table 22.6) [23]. The review found that the generator pocket was the site for 54% of the infections, while the SCS lead made up 17%, skin incision site 8%. Infection occurred in multiple sites 14% of the time. Methicillin-sensitive *Staphylococcus aureus* encompasses the majority of these infections, with *Pseudomonas aerugi-*

Table 22.5 Rates of implant-related pain for SCS

Publication	*N*	Pain over implant (%)	Publication type
Cameron 2004	2753	0.9	Review article
Turner 2004	830	5.8	Systematic review
Kumar 2006	410	1.2	Retrospective analysis
Kumar 2008	42	12	RCT
Mekhail 2011	707	12	Retrospective analysis
de Vos 2014	40	5	RCT
Total	4782	Range 0.9–12	
		Mean 6.15	
		95 CI 0.97–11.33	

Adapted from Eldabe et al. [23]

Table 22.6 Rate of infection for SCS

Publication	*N*	Infection (%)	Publication type
Cameron 2004	2972	3.4	Review article
Follett 2004	114	N/A	Retrospective review
Turner 2004	830	4.6	Systematic review
North 2005	45	6	RCT
Taylor 2005	112	6	Systematic review
Taylor 2006	66	4	Systematic review
Kumar 2006	410	3.4	Retrospective analysis
Kumar 2008	42	10	RCT
Mekhail 2011	527	4.5	Retrospective analysis
De Vos 2014	40	2.5	RCT
Slagen 2014	22	4.5	RCT
Total	5180	Range 2.5–10	
		Mean 4.89	
		95 CI 3.38–6.39	

Adapted from Eldabe et al. [23]
RCT Randomized control trial

nosa, *Staphylococcus epidermidis*, and methicillin-resistant *Staphylococcus aureus* occurring in lower frequency [21, 24]. It has been shown that smoking and obesity, i.e., having a body mass index of ≥30, were significant risk factors in developing SCS infections and were associated in 50% and 40% of patients, respectively [21]. Factors known to impede wound healing (e.g., obesity, smoking, diabetes, malnutrition, corticosteroid use, poor hygiene) should be assessed and discussed with the patient prior implanting a SCS [21, 23]. Techniques to prevent infection include preoperative *Staphylococcus aureus* screening, intranasal mupirocin ointment treatment for positive cultures, prophylactic antibiotics administration, strict adherence to sterile techniques, and wound hemostasis [21, 24]. Complete removal of the device and intravenous antibiotic treatment is often the treatment; however SCS implant revisions impart a significantly higher infection rate when compared to the initial operation (12.5% vs 1.3%; $p = 0.02$) [21, 23].

Iatrogenic dural puncture is a rare biological complication of SCS with reported incidence of 0–0.3% [23]. Headaches and CSF leaks can occur following dural puncture. Female, age (31–50 years old), prior history of dural puncture headaches, and perpendicular (rather than parallel) orientation of the bevel have been associated with the increased risk of dural puncture. Post-dural puncture headaches may be positional and may also be accompanied by neck pain, photophobia, diplopia, and tinnitus. The resultant CSF leak may collect at the site of lead anchoring, leading to discomfort at that area or lead migration. Activities of daily living may be hampered if symptoms from dural puncture is severe [23]. If initial conservative management, i.e., bed rest, does not resolve the symptoms, an epidural blood patch can be attempted [25]. If CSF leaks persists despite mentioned therapies, surgical exploration and closure is the definitive treatment [25, 26].

Neurological injury is the worst biological complication of SCS [23]. Immediate neurological insult can be caused by direct trauma secondary to needle puncture or lead placement done percutaneously or during surgery. Delayed neurological damage can result from nerve compression from either hematoma or abscess formation [23]. Although the rate of neurological injury continues to be maintained at a low rate, it is important to recognize any neurological deficits following a SCS implant so that emergent treatment can be instituted prior to irreversible neurological damage [21, 27].

Perhaps one of the greatest unknowns is why traditional SCS has a loss of efficacy over time. Hayek et al. reported 13.7% of their patients having loss of efficacy, and 39% had had their SCS

explanted (median time 19.62 months, 95% CI 18.02–33.27) and 16.1% had revisions [21]. These changes may be due to the result of cellular changes in tissue around the electrodes, such as buildup around the contacts, or temporary changes in the electrode positioning such as lead migration or postural changes. There are many reports in the literature of painful stimulation, ineffective stimulation, or loss of stimulation over time. However, high frequency SCS treatment has not demonstrated this same pattern of decline in response over time. As the technologies are advancing, we are seeing both a reduction in complications and enhanced efficacy of stimulation.

Rare Adverse Effects

Some rare adverse effects of spinal cord stimulation are a direct result of lead placement in the spinal column. Leads placed with the goal of stimulating the caudal segment of the spinal cord can cause micturition inhibition. This unexpected development of neurologic bladder and micturition dysfunction results simultaneously with the onset of pain relief, after the beginning of an electrical stimulation of the caudal segment of the spinal cord (T11–L1) [28]. The interruption of stimulation resolves the symptoms.

Gastrointestinal symptoms are the broadest category of rare adverse side effects. The symptoms range from severe nausea caused by the spinal cord stimulator to abdominal pain and constipation [28]. Constipation and distention are directly related to above paresthesia perceptual threshold. These symptoms often resolve after several weeks and are thought to be related to GI parasympathetic tone or antidromic activation of sensory afferents.

Scar tissue formation is another issue that results in adverse effects. One such issue is cervical cord compression due to delayed scarring around epidural electrodes used in spinal cord stimulation. In a study by Dam-Hieu et al., two surgeries were required to correct this issue [29]. The removal of the SCS alone was not effective. However, the removal of the scar tissue resulted in significant improvement of symptoms. Another similar complication is late-onset cervical myelopathy secondary to fibrous scar tissue formation around the spinal cord stimulation electrode [30]. A similar case was also reported as spinal cord compression from a foreign-body reaction to spinal cord stimulation [31]. An epidural mass causing significant cervical stenosis and spinal cord compression occurred in one case at the site of a previous SCS. Decompressive laminectomies and a resection of the mass were required.

It is important to understand that these are rare, isolated cases of SCS causing adverse effects. The aforementioned adverse effects are possible in an SCS implant and therefore must be monitored.

Evolving Technologies and the Future of SCS

Spinal cord stimulation originally consisted of monopolar leads connected to external generators to create the electric field around the spinal cord for the treatment of chronic pain. Since then we have expanded to fully implanted rechargeable batteries and leads have progressed from monopolar plates to multiple leads with multiple contacts allowing for up to 32 contacts. More impressive is that each contact has individual power sources to maximize precision targeting of pain. In addition to the continual improvements in technology, the field of SCS has expanded from stimulating only the spinal cord to also being applied to regions of the brain, now called deep brain stimulation (DBS), as well as peripheral nerve stimulation being applied to more peripheral structures like the dorsal root ganglia.

The paresthesia-free analgesia induced by high-frequency SCS therapy continues to yield strong clinical results. While the fundamental mechanism for SCS remains elusive, the unrefutable results of the therapy illuminate what could be a new and effective tool to help those suffering from chronic pain. Similarly, as we remain in the exploratory stages of therapies, recent data show that the definition of high frequency may change in the coming years. Multiple investigations have compared paresthesia-free SCS therapies at fre-

quencies of just 1 kHz to the effectiveness of traditional SCS therapy and have found improved analgesia responses [20]. These studies demonstrate that 10 kHz therapy may not be required to disrupt these pain pathways, and similar analgesia may be induced at much lower frequencies. More research is required as to define the optimal frequency and delivery mode which may potentially allow us to better titrate current therapy.

Similarly as we better illuminate the complexities of the neuronal and biological pain matrix, the proposition of "drug-enhanced spinal stimulation" therapy becomes a viable opportunity to further specify and personalize treatment strategies. It was demonstrated in animal studies that the SCS-induced analgesia was reversed by adding a GABA antagonist demonstrating the significance of GABA on SCS-mediated analgesia [22]. In response, a recent study performed on rats deemed "nonresponders" to SCS showed that following intrathecal GABA-B agonist treatment with Baclofen, a large majority of the subjects were transformed into responders [29]. Other studies investigating serotonin have shown that the effect of SCS at subthreshold was made effective upon administration of typically non-analgesic doses of serotonin linking SCS to the serotonin pathway. Additional studies have shown that serotonin and substance P are released following SCS. A more complete list demonstrating the efficacy of SCS with cotreatment of various neurotransmitters is summarized in Table 22.7 [24]. This data provides a potential field of neurobiological supplementation therapy as an adjunct to further enhance SCS treatment in the appropriate patient.

Table 22.7 Effect of various spinal originating transmitters on efficacy of SCS

Spinal neurotransmitter	Effect of cotreatment with SCS
Acetylcholine	Increased
Adenosine	Increased
GABA	Increased
Norepinephrine	Increased
Serotonin	Increased
Substance-P	Increased
Aspartate	Decreased
Glutamate	Decreased

Adapted from Wada and Kawai [32]

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