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Introduction to the Programming of Deep Brain Stimulators

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Abstract: The clinical success of deep brain stimulation (DBS) for treating Parkinson's disease, tremor, or dystonia critically depends on the quality of postoperative neurologic management. Movement disorder specialists becoming involved with this therapy need to acquire new skills to optimally adapt stimulation parameters and medication after implantation of a DBS system. In clinical practice, the infinite number of possible parameter settings in DBS can be reduced to few relevant combinations. In this article, the authors describe a general scheme of selecting stimulation parameters in DBS and provide clinical and neurophysiological arguments for such a standardized algorithm. They also describe noninvasive technical trouble shooting by using programming features of the commercially available neurostimulation devices. © 2002 Movement Disorder Society

Key words: deep brain stimulation; Parkinson's disease; dystonia; tremor

Neurophysiologists have used extracellular electrical stimulation of cortex or deep brain structures for over a century as a tool to study brain physiology. Electrical stimulation evokes behavioral effects by exciting brain cells. A negative (cathodal) stimulus applied outside a neuron or a positive (anodal) stimulus inside a neuron reduce the membrane resting potential and may depolarize the cell up to the threshold for inducing an action potential. The behavioral effects of brain stimulation depend on the exact location of the stimulation electrode, the choice of stimulation parameters, and on biological factors that cannot be controlled such as the histology of the neural tissue being stimulated (e.g., predominance of cell bodies, dendrites, large- or small-diameter axons). Electrical stimulation in general is more likely to activate large myelinated fibres before small axons or cell bodies, axons near the cathode before those near the anode, and axons oriented parallel to the electrode before axons oriented transversely.[1–3] Electrode polarity, pulse width, and current amplitude are stimulation parameters determining which neural elements in the surround of a stimulating electrode are being recruited.[4] When using trains of stimulation, pulse rate and train duration are additional factors influencing the behavioral response.[4,5] Therapeutic deep brain stimulation (DBS) must follow the same physiological principles as experimental extracellular stimulation, but to date, it is not certain which neural elements are being targeted by DBS. First experimental evidence suggests that DBS effects may primarily be mediated by stimulation of large myelinated axons[6] (a survey is also given in this supplement[7]). For setting stimulation parameters in DBS, it is, therefore, advisable to have some understanding of the basic physiology of electrical stimulation and the interaction of different electrical parameters with respect to the response. The following sections describe for each adjustable parameter in DBS these fundamental effects, discuss device-related limitations, and give general suggestions for the initial settings. Our suggestions are oriented toward the following principle goals of DBS programming: (1) to maximize symptom suppression, (2) to minimize side effects, and (3) to maximize neurostimulator battery life.

Currently, Medtronic (Minneapolis, MN) is the only manufacturer providing clinically approved DBS devices. The commercial DBS systems consist of a quadripolar electrode with an intercontact distance of 1.5 (model 3387) or 0.5 mm (model 3389), an extension cable and an internal pulse generator (IPG) either controlling one (Itrel II, Soletra) or two (Kinetra) DBS electrodes. Current is delivered through cylindric electrode contacts of 1.27-mm diameter and 1.5-mm length resulting in an electrode surface of 5.99 mm^2. The relevant

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stimulation parameters, which can be controlled telemetrically by use of an external console programmer (model 7432) after implantation of the IPG, are electrode polarity, amplitude, pulse width, and frequency.

ELECTRODE POLARITY

Each electrode contact can be programmed as anode or cathode in bipolar settings or as cathode for monopolar stimulation against the neurostimulator case. Monopolar stimulation provides a radial current diffusion, covering an approximately spherical space around the stimulating electrode.[3] Bipolar stimulation creates a narrower and more focused current field with a maximal effect near the cathode.[3] By reducing diffusion into adjacent structures, it may be possible to avoid side effects of monopolar stimulation. One should, however, always try monopolar stimulation first, because it usually requires a lower stimulation intensity than bipolar stimulation to achieve the same clinical benefit.[8] Normally, a single cathode is chosen for DBS, although it may be useful in some cases to activate two adjacent contacts where a broader current diffusion is desired.

AMPLITUDE

With increasing amplitude, neural elements in a gradually increasing distance from the electrode are being stimulated. Ranck[3] summarized in his review several experimental studies on this current-distance relationship. According to these data, a monopolar cathodic pulse of 200-μsec pulse duration and a current amplitude of 1 mA could excite neural elements up to a distance of 2 mm. The commercial IPGs provide a constant voltage stimulation. Therapeutic amplitudes for DBS normally range between 1 and 3.5 V at a pulse width between 60 and 210 μsec (rarely above) for the different stereotactic targets. For a standard tissue impedance in the range of 1,000 Ω, a current amplitude of 1 mA, therefore, falls within the therapeutic range of DBS. The data provided by Ranck,[3] however, may at best be used as a rough approximation of the true current-distance relation of DBS, because electrode design and biophysical properties of the neural elements mediating the behavioral effect (e.g., axon, cell body) have a strong impact.

The commercial IPGs of Medtronic, allow one to vary voltage in 0.1 V steps between 0 and 10.5 V. An important technical issue has to be considered, i.e., when programming an Itrel II or Soletra neurostimulator: The electrical current consumption of these neurostimulators is linear up to 3.6 V and rises abruptly above 3.6 V and 7.3 V, because a voltage doubler or tripler circuit are activated within the neurostimulator. Thus, an increase in amplitude from 3.6 to 3.7 V may only result in a minimal change of clinical efficacy, yet significantly increases battery drain and shortens battery life by approximately half. Therefore, the voltage should not be increased above 3.6 V. Alternatively, the pulse width may be increased, if necessary, with a downward adjustment of the amplitude. A different electrical circuitry allows one to raise voltage in the Kinetra IPG to the maximal amplitude of 10.5 V with a linear increase in current consumption throughout the whole range.

PULSE WIDTH

Medtronic IPGs allow one to vary pulse width in steps between 60 and 450 μsec. The current required to stimulate a neural element decreases as pulse width increases, but not in a simple linear way. The relation between necessary current and the duration of the pulse that gives the same response usually fits the empirical equation $I = I_r(1\text{-}C/t)$, where I is the current (or voltage), I_r is the rheobase current, t is time and C is chronaxie.[3] Rheobase current is the minimal amount of current necessary to stimulate with a long pulse width. Chronaxie is the time on the strength duration curve for twice rheobase current (Fig. 1). Chronaxies for DBS effects have been estimated to be approximately 65 μsec for thalamic and around 75 μsec for pallidal stimulation.[6] These findings suggest that one should always screen for DBS effects at the lowest possible pulse width of 60 μsec. Increasing pulse width above 210 μsec or more could bring the amplitude threshold for clinical effects close to the rheobase current and, therefore, leave little range for a differential setting. This strength-duration relationship should especially be

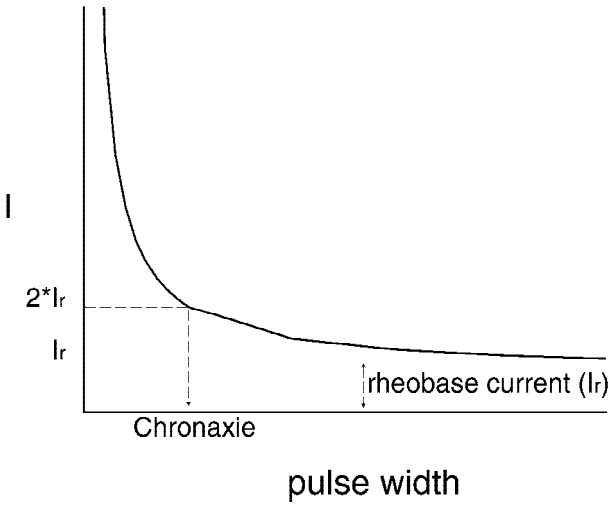

FIG. 1. The nonlinear relationship between pulse width and current necessary to stimulate a neural element. Rheobase current (I_r) is the minimal amount of current necessary to stimulate with a long pulse width. Chronaxie is the time on the strength duration curve for twice rheobase current.

kept in mind when side effects arise from unintended costimulation of adjacent fiber tracts. Such costimulation leading, e.g., to dysarthria in subthalamic nucleus (STN) DBS or ataxia in thalamic DBS, is more likely to occur at long pulse durations, where strength–duration curves of neural elements with different excitability run closer or even intersect. An example of a patient with thalamic deep brain stimulation is illustrated in Figure 2, in whom a further increase in pulse width progressively narrowed the therapeutic amplitude window between tremor suppression and induction of ataxia.

Reasons for increasing pulse width beyond the initial setting of 60 μsec could be an unsatisfactory clinical response after increasing voltage to the limit of 3.6 V before reaching the energy doubling point in Itrel II and Soletra neurostimulators or to the amplitude maximum of 10.5 V in a Kinetra IPG. In these cases, pulse width should be set to the next increment of 90 μsec. The amplitude may need to be lowered in case of side effects. In our own experience, the pulse width for stimulation of the subthalamic nucleus is 60–90 μsec, for thalamic stimulation 60–120 μsec, and for pallidal stimulation usually higher, up to 210 μsec. The necessity to further increase pulse width due to unsatisfactory clinical results at maximal voltage levels usually indicates a misplaced electrode. This approach is warranted if an additional clinical benefit is achieved without induction of side effects, but surgical repositioning should also be considered, because battery drain increases proportionally and may cause frequent IPG exchanges.

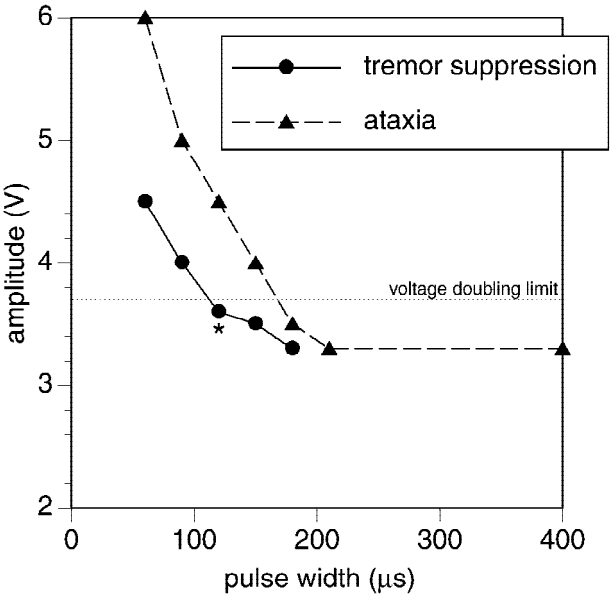

FIG. 2. In a patient with thalamic deep brain stimulation, strength-duration curves were determined for tremor suppression and the induction of ataxia as a limiting side effect. With increasing pulse width, the threshold for inducing ataxia approaches the threshold for tremor suppression until both curves intersect. The figure illustrates the reason for choosing a pulse width of 120 μsec for chronic stimulation (asterisk) in this case, which allows one to achieve satisfactory symptom suppression below the critical voltage doubling point at 3.7 V and with the largest possible therapeutic width before inducing ataxia.

FREQUENCY

Pulse frequency can be set between 2 and 185 Hz in the Itrel II or Soletra neurostimulator and between 2 and 250 Hz in the Kinetra neurostimulator. The lesioning-like effect of deep brain stimulation is only observed at high frequencies above 100 Hz with a fairly abrupt threshold.[9,10] This nonlinear frequency dependency of ventralis intermedius (Vim), STN, and globus pallidus pars interna (GPi) stimulation effects differs from the usual encoding of signal magnitude by neuronal firing rate. For example, increasing the frequency of stimulation in optic tract or medial lemniscus results in progressively stronger perception of phosphenes or dysesthesias. Low-frequency stimulation of the pyramidal tract, likewise, causes muscle contractions with each individual stimulus. At higher frequencies, the individual muscle twitches start to fuse and change into a tetanic muscle contraction. A lesioning-like effect causing scotomas, anesthesia, or paralysis has not been observed in these structures during high-frequency stimulation and seems to be specific to therapeutic thalamic or basal ganglia stimulation.

Benabid and colleagues have studied the amplitude-frequency relationship for the anti-tremor effect of thalamic stimulation systematically.[10] At frequencies below 50 Hz, no effect was observed. Above 50 Hz tremor amplitude could be decreased at progressively lower stimulation intensity until a plateau was reached around 130 Hz. A further increase from 200 to 10,000 Hz, by using an external stimulator, did not lead to a further increase in the anti-tremor effect. The clinical effect of STN stimulation on akinesia and rigidity was studied with similar results.[11] Rigidity and akinesia were only reduced by stimulation frequencies above 50 Hz. The effect rose linearly with increasing frequency and was almost maximum around 130 Hz. There was a further small, nonlinear increase in efficacy above 130 Hz, up to the maximum frequency of the Itrel II neurostimulator (185 Hz).

In a case report, Kumar and colleagues described an optimal suppression of dystonia by pallidal stimulation in the 50 Hz frequency range.[12] This observation should be interpreted with caution, because suppression of dystonia was achieved in all other reports[13–18] by parameter settings that were comparable to those in pallidal stimulation for Parkinson's disease.

As a compromise between clinical efficacy and power consumption, we usually set stimulation frequency to 130 Hz. Exceptional reasons for changing this fixed rate may be an unsatisfactory clinical response, that cannot be improved by an increase in voltage or pulse width without causing side effects by unintended current spread. In these rare instances (usually tremor cases) a further increase in frequency may improve clinical benefit without increasing current diffusion into adjacent structures.

BASIC ALGORITHM FOR DBS PROGRAMMING

The most important step during postoperative programming is to determine for each of the four electrode contacts the clinical efficacy and side effects to acute stimulation. These initial test results will serve as a reference for all future adaptations of DBS parameters. The acute testing is usually a good predictor for the long-term clinical benefit, and changes of the electrode setting are rarely necessary if the initial testing is properly done and documented. The examination should take place in a stable *off*-drug condition to prevent medication effects from interfering with DBS effects. Pulse width is set to 60 μsec and frequency to 130 Hz. Both parameters are kept constant throughout the testing period. Then, for each electrode contact the amplitude threshold for inducing a clinical response or side effect is determined by using monopolar stimulation and a stepwise increase in amplitude (0.2–0.5 V).

The target symptoms that are examined after each increment to evaluate the clinical response may vary, depending on the stimulated structure and the individual symptomatology. Moreover, the time course of the stimulation response can substantially differ between clinical symptoms and predispose some more to acute clinical testing than others. Rigidity usually responds within seconds to STN or GPi stimulation and can be examined reliably even if patient cooperation is poor. Other standardized motor tasks such as alternating movements (items 23–26 of the Unified Parkinson's Disease Rating Scale motor scale) or tremor may be used as additional criteria in patients with advanced Parkinson's disease. We usually examine upper limb tremor in the three conditions "rest" (with supported limbs), "posture" (wingbeating position), and "action" (finger-to-finger or finger-to-nose test). A provoking task such as backward counting may be useful if tremor severity fluctuates. Acute testing of clinical effects in dystonia may be more difficult, because the stimulation response may develop over a longer time period. Often, however, small changes in mobile dystonia are visible acutely or the patient feels a reduction in muscle tension before the examiner can observe the effect.

If a clinical response is observed before evoking side effects, we further increase the amplitude to determine the threshold for adverse effects. The electrode contact with the lowest threshold for inducing therapeutic effects and the largest therapeutic width is finally selected for chronic stimulation. The initial setting for chronic stimulation is monopolar with a single cathode, 60-μsec pulse width (often higher for pallidal stimulation, i.e., 90–120 μsec), 130 Hz frequency, and a variable amplitude. In Figure 3, a basic algorithm is introduced: how to modify these initial parameter settings during the further postoperative course. As a rule, chronic stimulation should be initiated in the morning, never in the evening or before weekends, unless the patient is under observation and the treating physician is available. Delayed complications such as severe dyskinesias in STN stimulation for Parkinson's disease may occur hours after initiating the stimulation or increasing the amplitude or pulse width.

TECHNICAL TROUBLE-SHOOTING

Neurostimulation devices of Medtronic, Inc., provide some monitoring features, which are useful to distinguish device-related problems from other forms of therapeutic failure. These features consist in impedance measurement, control of the battery status, and a device log containing counters of magnet activations and stimulation time. A device-related problem can be suspected when no stimulation response is encountered during the initial postoperative testing, when patients experience a sudden decrease in clinical efficacy during chronic stimulation, or when intermittent side effects of stimulation occur. The following section describes methods for noninvasive trouble shooting and programming steps to be taken in these events.

The most frequent cause of a sudden decrease in symptom suppression is an accidental turning OFF of one or both neurostimulators, which is easily recognized when reviewing the stimulation parameters. Unless the patient used a magnet to operate the neurostimulator, electromagnetic interference is likely the cause. Unusually high numbers of ON-OFF cycles, in a range of > 25 events in the neurostimulator log also suggest this cause. Therefore, the magnet activation counter should routinely be set to zero at the end of each follow-up visit, to allow detection of such unusually high activation cycles. Possible sources of electromagnetic interference are household devices when used in close proximity (distances of less than 10 cm are typically necessary for an accidental activation of the magnetic switch), such as

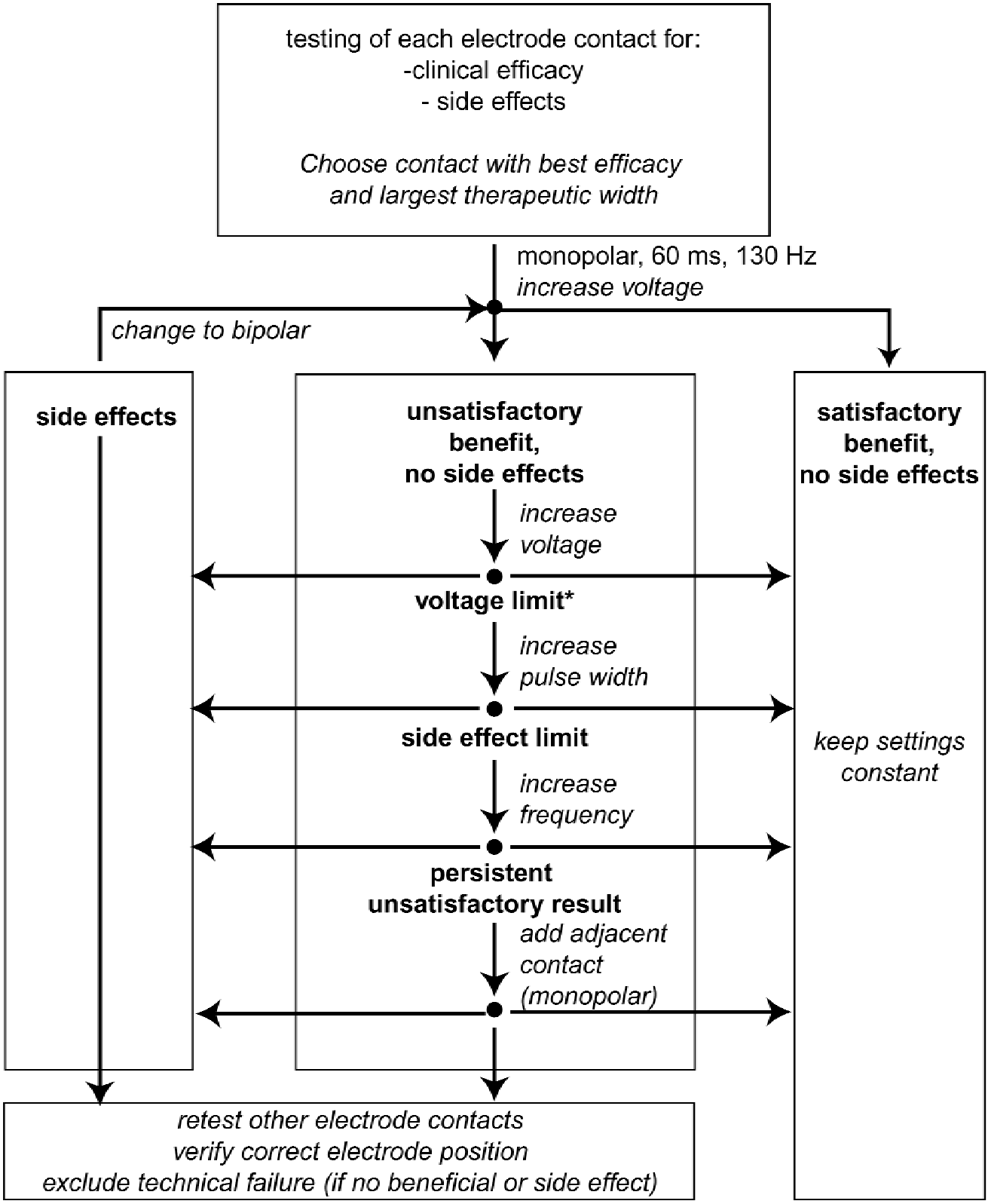

FIG. 3. Basic algorithm for setting deep brain stimulation parameters during the postoperative course. *Voltage doubling point (3.6 V) in Itrel II and Soletra (Medtronic) neurostimulators or maximal voltage (10.5 V) in Kinetra neurostimulators (Medtronic).

electric shavers, electric toothbrushes, microwaves, mixers, electric drills, or other power tools. Electromagnetic interference has occasionally been reported due to antitheft devices in department stores or metal detectors, e.g., in airports. Another important source of electromagnetic interference is the influence of static magnetic fields, for example, from magnets in loudspeakers. A detailed patient history, from the time the patient first noted an increase in symptoms, usually helps to narrow down the source of electromagnetic interference. If patients with a Kinetra neurostimulator experience problems related to electromagnetic interference, the neurostimulator's reed switch should be programmed to a disabled setting. Patients with an Itrel II or Soletra neurostimulator should be educated in how to use the magnet and an AM radio to check the neurostimulation status.

In Itrel II neurostimulators, a sudden decrease in symptom suppression may occur when patients accidentally activate the magnet amplitude, which is programmed lower than the normal amplitude. To prevent this problem, we usually set normal and magnet amplitude to the same value at the end of each programming session.

If a sudden loss of efficacy is experienced and accidental turning OFF of the neurostimulator can be excluded, a system problem is the likely cause. The following approach helps to identify the cause of the problem:

Measure impedance of all electrodes. To measure the impedance, select the menu item *IPG output*, then *Imp* on the physician programmer. It is useful to measure the impedance in a unipolar instead of a bipolar configuration so that the impedance value can be directly assigned to the respective electrode. The standard setting of 1 V, 210 μsec, and 30 Hz should be used for maximum accuracy in impedance measurement (Itrel II, Soletra). These settings will also allow long-term comparison of impedances in one patient. Impedances close to 2,000 Ohms can only be measured accurately at relatively high amplitudes or pulse widths. However, it is possible to use the therapeutic stimulation parameters for impedance measurements if the impedance is within a lower range. Typically the measured impedances lie in a range from 500 to 1,500 Ohms. Unfortunately, the Itrel II neurostimulator does not read values at impedances greater than 2,000 Ohms. (The Kinetra neurostimulator reads values > 4,000 Ohms.) At an impedance > 2,000 Ohms, a connection problem, a broken cable, or a lead fracture may be suspected.

Measure battery load. To rule out unusually high tissue impedance, the battery load should be measured for each electrode by using the function *IPG Battery* on the physician programmer. If the open-circuit current of the neurostimulator battery (Itrel II neurostimulator 7μA and Kinetra neurostimulator 15 μA) does not increase while carefully raising the amplitude to a maximum of 3 to 5 V, an interrupted electrical circuit is very likely. An impedance below 50 Ohms and a high battery drain > 2,000 μA indicate a short circuit in the system.

Palpation of system components. A noninvasive approach to detect intermittent stimulation is palpation of the implanted components with stimulation ON to identify the location of a loose connection. If the patient reports tingling pain or dysaesthesias at a location near the implanted system, damage to the insulation and an exposed conductor should be suspected.

Radio test. When stimulation is turned on, the Itrel II, Soletra, and Kinetra neurostimulators produce a signal in the medium-frequency range (500–550 kHz), which can be received as a continuous hum with a radio. To use this method of testing, a preferably small and battery-operated AM radio receiver is held directly over the neurostimulator or along the cable on the neck or head. The volume of the buzz is dependent on the stimulation amplitude and is best heard with unipolar stimulation. The pitch of the hum varies with the stimulation frequency. For better differentiation of right and left stimulation systems, the two Itrel II or Soletra neurostimulators may be programmed to different stimulation frequencies (e.g., 130 and 145 Hz). A decreased buzzing sound helps to localize reduced or interrupted current flow.

X-ray. If a disconnection problem is suspected from impedance measurements, plain X-rays of the implanted system components (lead, extension, and neurostimulator) should be obtained. A broken lead, dislodgement of the lead from the extension connector, or gross damages to the insulation may be visible on these scans and help to narrow down the location of the system problem. If the impedances are within a normal range, a problem in the electrical circuit can be excluded as a cause of no or insufficient stimulation effect. The most likely cause in this case is a misplaced or dislocated lead. *Gross dislocations*, which may occasionally occur through very strong tension during implantation of the neurostimulator, can be detected in a two-plane radiograph of the skull. If a dislocation is confirmed, a surgical revision is necessary to reposition or replace the leads.

If the noninvasive procedures suggest a system complication that affects the electrical circuitry in all electrodes, or if adequate symptom relief is not achieved with any of the remaining intact electrodes, a surgical revision is necessary. In the revision, as with the initial implantation, the neurosurgeon and the neurologist should cooperate. If it was possible to narrow down the suspected

location of the technical defect through palpation or X-ray, the system should first be exposed and inspected at this location. In all other cases, the connector between the lead and the extension should be exposed under local anesthesia. Next the connection should be inspected, and the connector should be opened. Then the electrode should be connected by means of an external stimulation cable to a Medtronic Test Stimulator (external stimulation device). If typical effects or side effects can be induced with test stimulation, the lead is not the cause of the problem; therefore, the extension should be replaced. To ensure successful replacement, the impedances need to be checked again intraoperatively, after reconnection of the system. If no effects or side effects can be induced during external test stimulation, despite high amplitudes, the lead is probably damaged and operative replacement is advocated.

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