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Different Modalities and Parameters in Spinal Cord Stimulation Treatment

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Abstract. Electrical stimulation to treat diseases can be tranced back to the pharaonic era. Since then, people have found using the electrical pulse generated by electric cat-fish can mange the patient's pain effectively. Foreign studies started early, and the technology was relatively mature. Spinal cord stimulation was produced in the 1960s by inserting stimulating electrodes into the spinal canal's epidural area. At the same time, the pulse generator was implanted subcutaneously to achieve the purpose of pain treatment with electrical pulses. This article will introduce three main types of stimulation mechanism: constant voltage stimulation, constant current stimulation and activation of the charge mode. Compare the impact of the given stimulus with the design's complexity. However, because the electrode impedance varies with position and time, it is difficult to precisely control the charge of the stimulus, resulting in difficulty in controlling the net charge balance. Secondly, introduce the different parameters and their role in spinal cord stimulation, including the threshold of the cell membrane decide if it can generate the action potential. And the relationship between stimulation amplitude and pulse width, the current intensity is gradually reduced with the grow of stimulation pulse width. And the frequency and waveform, these parameters influence each other and are considered as the most important factors for the patients' pain management in SCS.

Keywords: Spinal cord stimulation; Neurostimulation; Bioelectronics.

1. Introduction

The central nervous system is a sophisticated information processing and control system made up of the brain and spinal cord. This system plays a significant role in our daily lives, controlling spontaneous movements and regulating involuntary activities like breathing. The spinal cord runs from the base of the brain to the midline of the back and the end of the spine as a central nervous system component. The spinal cord acts as a means of transmitting impulses to the body and a bridge for information exchange between the body and the brain. Therefore, the degree of suffering that spinal cord injury victims have will be seriously reduced. The World Health Organization estimates that spinal cord injuries affect at least 250,000 people annually [1]. Nerve stimulation has been widely used in implantable biomedical devices to establish the connection between brain and limbs by offering a balanced charge to cause biological tissues' action potentials, which help people regain functions they may have lost. Spinal cord stimulation is considered to be the most promising technology to treat spinal cord injury and help patients establish the connection between brain and limbs.

So far, based on the stimulation mechanism of SCS, there are three categories into which it can be separated: constant current stimulation (CCS), constant voltage stimulation (CVS) and charge mode stimulation [2].

CVS is the most common used stimulation protocol as it can provide high efficiency stimulation directly. The design is relatively simple. However, it is difficult to precisely control the electric charge of the stimulation. Because of the electrode impedance varies with locations and times, controlling the net charge balance is challenging. Keeping net charge accumulation balance is one of the most important factors for implantable devices. Charge will be accumulated in the stimulated nerve tissue if it is not precise enough, even cause the changes in the PH of enchylema when the amount of charge accumulated exceeds the safe range, resulting in damage to body.

As opposed to VCS, CCS can control the net charge balance precisely. However, it has a relatively low stimulation efficiency. This type of stimulation typically requires a series of current sources. A significant voltage drop at the current source will exist during the stimulation process, and consuming energy leads to inefficient stimulation. CCS was more and more popular than traditional VCS mainly because it responds quickly to transient changes and can avoid tissue damage caused by excessive charge input into human tissues, as well as other safety considerations.

Charge mode stimulation refers to one mode in which current is delivered in pulses, stored, and released in the form of charge. Normally, it occupies a very large chip area [3], mainly because the circuit must be complex enough to satisfy the store and release of the charge. Through charge mode, the current can be delivered through electrodes to the nerve tissue to form a pulse, while the charge is accumulated and then released at the end of the pulse period. The effect of pulsating charge stimulation on biological tissues is still unclear. It needs further study and investigation, including an in-depth investigation of biological effects, stimulation parameter optimization, and comparison with other stimulation modalities.

Next, this article will introduce different stimulus parameter. Starting with the Gate Control theory, which had a historic impact on the pain management in SCS. And the stimulus amplitude, pulse width, frequency, and waveforms with their roles in SCS.

2. Stimulus parameters

2.1. Section Headings Threshold and Gate Control theory

The neural response to the external electrical stimulation should be considered an all-or-no response. The nerve membrane charged linearly for the smaller electrical stimulus, generating no action potential. When the stimulus is increased to the threshold, sodium ions flow influx, and the cell membrane generates action potential. Then, the action potential travels along the nerve fiber, stimulating the axons to release neurotransmitters that act on the target or next neuron [4]. This artificial generation of action potentials is the working basis of all the electrical stimulation systems.

Applied into spinal cord electrical stimulation, the gate control idea was initially put forth by Melzack and Wall in 1965 [5]. This notion hypothesized a neural gate in the glial area of the spinal cord's dorsal horn, which can be opened or closed to different degrees. The outer peripheral nervous system contains no myelin fine fiber (C - fiber) and a small amount of fine fiber containing myelin (A fiber), when there is too much crude fiber afferent nerve activity, neurological "door" shut down. Therefore, based on the gate control theory, electrical stimulation that specifically activates coarse afferent fibers can selectively close the gate and reduce or eliminate pain input to the spinal cord. However, studies indicate that the mechanisms underlying the effectiveness of SCS are notably intricate. SCS operates by locally modifying the excitability of wide-dynamic-range neurons, enhancing physiological inhibitory processes, and influencing the activity of various neurotransmitters. These neurotransmitters include GABA, glutamate, adenosine, acetylcholine and others [6]. Also, differences in excitability of different nerves can lead to responses with different effects [7].

2.2. Page Numbers Stimulus amplitude and pulse width

The smallest unit in spinal cord stimulation is a pulse with two type information. The current amplitude(mA) and pulse width(μs).

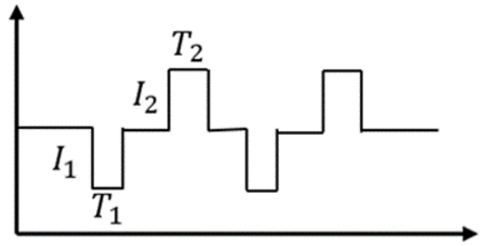

Fig. 1 Waveforms of biphasic charge (original)

As the Figure 1 above, shows the way of bidirectional current stimulation (biphasic charge). After one pulse, an equivalent current always flows in the opposite direction to equal the net charge accumulation balance requirement. Mismatched bidirectional current pulses will cause residual charge resulting in DC current flowing into tissues and causing tissue damage [8].

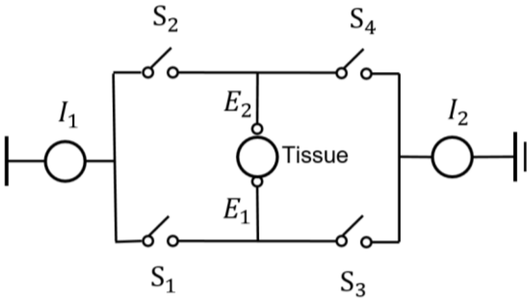

Fig. 2 An example of circuit for bidirectional current stimulation (original)

The schematic diagram in Figure 2 illustrates bidirectional current stimulation (biphasic charge). When closing the switches S1 and S4, along with switches S2 and S3 off, the current shows the direction of flow from electrode 1 through human tissue to electrode 2. Conversely, when the off and closed switches are exchanged, the opposite is bound to happen, flowing from electrode 2 through human tissue back to electrode 1. To ensure zero net charge accumulation, the amount of charge passing through the tissue must remain equal for both forward and reverse currents. It needs to satisfy the equation:

$$I_1 \times T_1 = I_2 \times T_2 \tag{1}$$

Where I mean the current pulse amplitude and T represents the pulse width. Serial number 1 means the forward path (from electrode 1 to electrode 2), number 2 vice versa.

Also, the current intensity needed to stimulate the nerve is lower than that needed to stimulate the muscle. The relationship between stimulus intensity and pulse width is expressed as follows:

$$I_{\text{th}} = \frac{I_{\text{rh}}}{1-\exp^{(-PW/\ln(2)T_{\text{ch}})}} \tag{2}$$

Among this, I_{th} is the threshold current amplitude; I_{rh} means the basic current amplitude, when the pulse width is infinite, that is the current needed to stimulate the neuron.T_{ch} represents the pulse width required when the stimulation current amplitude is as twice as the basal current amplitude.

2.3. Stimulus frequency

Stimulus frequency is the number of pulses per second. It can be changeable to meet the need of different therapies and patients. In general, SCS system generate the current at a frequency from 40 to 100Hz, producing paresthesia due to abnormal charge balance [9]. The electro array clinically covered 12 mm^2area, and approximately 6 mm interval to apart each electrode [10]. The study by Holsheimer proved that in the usual case, the paresthesia threshold always possesses a relatively narrow ratio range and are connected to dorsal root stimulation [11]. This also leads to the separation between the spinal cord and the epidural electrode should be small enough to make sure the threshold for dorsal column stimulation is less than discomfort threshold [11]. Many researches showed that stimulus frequency is one of the most important factors for pain management in SCS patients. Low-frequency therapy (2–10 Hz) stimulates the μ-opioid receptor pathways, while high-frequency therapy (~100 Hz) is believed to stimulate endogenous δ-opioid systems instead [12]. Nevro® has developed a unique way using a high-frequency method of 10kHz, which has the advantages of having the better pain relief on specific areas of the back [13]. And avoid the tingling feeling that traditional spinal cord stimulation devices often produce. Sato KL et al. found the stimulation frequency below 60Hz participating more in endogenous opioid release due to it can accelerate the transmitter combing with μ-opioid receptors, while the relatively high frequency part has some connection to the activation of the δ-opioid system [14]. The threshold can be increased by using morphine-tolerant method and has the effect of preventing analgesia generated by SCS in different frequency [14]. The much higher frequency, 500Hz for instance, can trigger and influence the blood flow level in peripheral nerve system [15]. However, it will decrease the level of conduction characteristics of afferent sensory neurons (1000Hz) [16]. One thing needs to emphasize is when discussing the neural stimulation, stimulus intensity and pulse width need to be considered simultaneously as they relate to each other.

2.4. Stimulus waveform

When choosing the stimulus waveform, our main considerations is efficacy, safety and corrosion. Merrill at al compare safety and efficacy between different waveforms [17], as shown in the figure, "+++" means the best effect and performance (highest efficiency, minimal tissue damage or electrode corrosion). It can be seen that the monophasic pulse has the highest stimulation efficiency, but the tissue damage is the greatest due to charge accumulation. According to the previous description in order to avoid the net accumulation of charge stimulation of the current pulse using biphasic matching of the current pulse, like (b)(c)(d)(e)(f) in Figure 3. The stimulus waveform generally consists of two phases: the cathodal and the anodal. When cathode phase depolarization occurs, generating an action potential and induces a muscle response followed by an anode phase that removes charge accumulation.

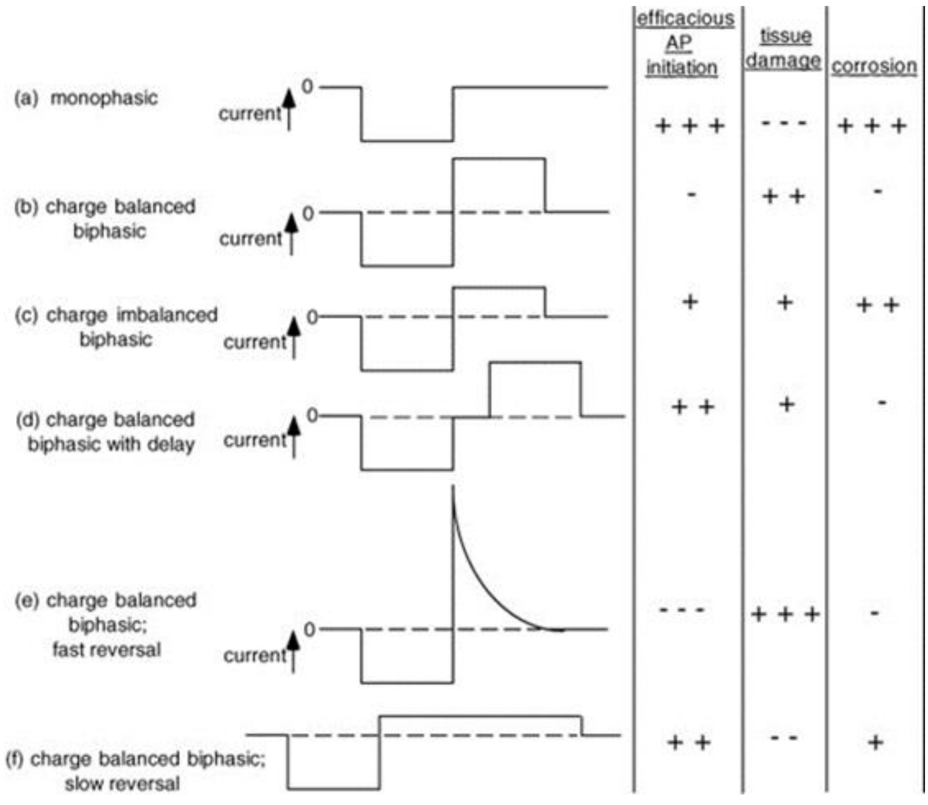

Fig. 3 Different type of charge and their performance tests [17]

As the current in figure (b)(c)(e)(f) changes from positive to negative directly at an instant, the voltage threshold of the nerve membrane will be polarized at an instant, resulting in tissue damage. Therefore, only the waveform (d) meets the safety requirements. The necessary time before the positive and negative current pulses in (d) is called the interphase interval, and this delay does not affect the action potential's spread at the stimulation site. And the interval time is mainly determined by the product of the amplitude of the positive and negative pulses and the stimulation time, that is the amount of charge.

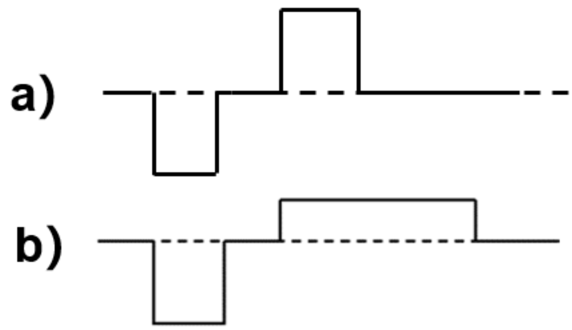

Fig. 4 Two types of charge with delay (original)

In Ativanichayaphong T’s study, it compared with two balanced charge waveforms, as (a) and (b) in Figure 4 [18]. The result showed that the degree of electrode corrosion in (b) is smaller. It can be concluded that the pulses with larger width and smaller amplitude tend to have better performance in electrode corrosion. Therefore, it is most appropriate to select (b) for the stimulation waveform in terms of efficacy, safety and electrode corrosion.

3. Conclusion

In conclusion, the history of electrical stimulation for disease treatment dates back to ancient times, with significant advancements ultimately resulting in the creation of SCS in the 1960s. SCS has witnessed widespread adoption throughout the past decade, with over 50,000 clinical cases annually. This paper has outlined three main types of stimulation mechanisms – constant voltage, constant current, and charge mode stimulation. No matter which stimulation patterns, their safety, efficiency are always the main topics for discussion and being aware of the parameters is equally significant. Furthermore, it has discussed the various parameters involved in SCS and their interplay, emphasizing their critical importance in therapy to individual patient needs.

In the future development of SCS, the service life will be one of the main limitations, depending on the service life of chemical batteries. The key to extending the battery life is to expand the battery power while reducing the battery's size and weight. The solution to achieve this goal is to use rechargeable batteries, so further investigation is required in the future to remedy the shortcomings of increasing the size of the stimulation itself. Another factor needs to be improved is the safety. Since it is implanted in human tissue, its safety is the ultimate requirement compared with general electronic devices. It is generally difficult to replace one-time implanted products. Once safety problems occur, the consequences are serious. Hence, the probability of failure of electronic components, such as short circuit or break of original connection, damage of wire insulation layer and some other problems needs to be minimized.

Authors Contribution

The authors’ names were listed in alphabetical order. Jiacheng Cai is the first author and Zhide Zheng is the second author.

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