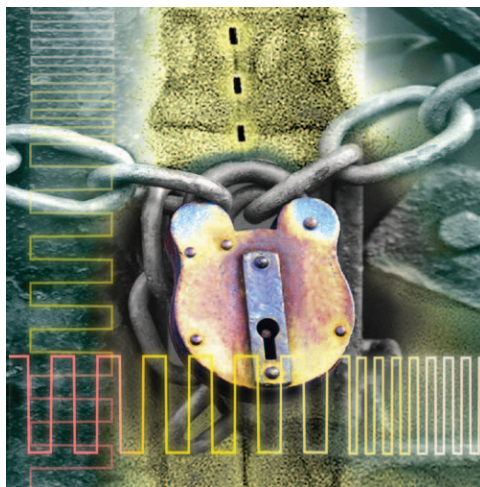


# Spinal Cord Stimulation

## Does Frequency Matter?

**S**PINAL cord stimulation was first described in 1967 in an intriguing case report provided by Shealy *et al.*<sup>1</sup> This first case involved the relief from cancer-related pain using a surgically implanted electrode sutured to the dura to provide stimulation of the dorsal columns. Although the entire treatment was only for approximately 1 day before the patient's demise, stimulation using 10–50 Hz current provided pain relief to this unfortunate individual. This work followed the slightly earlier publication of Melzac and Wall's gate control theory<sup>2</sup> and might be regarded as one of the earliest clinical applications of that hypothesis. Since that time spinal cord stimulation has become far more sophisticated; clinicians and patients are now able to select several different types of pulse generators and electrode styles. Particularly important advances have been made in the use of multiple electrodes, the design of the contacts, and in the availability of different parameters of current delivery. Likewise, the indications have expanded to include various forms of neuropathic pain, mixed-type pain such as that associated with failed back surgery syndrome, as well as pain from ischemic limbs and myocardium.<sup>3–5</sup> Despite the expanding use of this form of therapy, the precise mechanisms underlying the analgesic effects remain unclear, and are probably multiple. Furthermore, many patients, who would otherwise seem to be good candidates for spinal cord stimulation, fail stimulation trials either because the approach does not



***“[The] mix of success and failure of spinal cord stimulation raises the question of whether we are using the optimal stimulation parameters ...”***

provide pain relief or because the electrically induced paresthesias overlapping the painful region are found to be unacceptably uncomfortable for the patient. This mix of success and failure of spinal cord stimulation raises the question of whether we are using the optimal stimulation parameters in treating our patients. Using a rat model of spinal cord stimulation, Shechter *et al.*<sup>6</sup> in this month's ANESTHESIOLOGY demonstrate that the frequency of stimulation may be a critical factor.

Recently, reports have begun to appear describing results of the use of high-frequency spinal cord stimulation (1–10 kHz), frequencies well above the firing rates supported by most neurons. The touted benefits of this technology include the lack of uncomfortable paresthesias and perhaps a broader spectrum of analgesic activity. Results of available clinical trials are not entirely clear at this time.

For example, a reasonably large European study reported that 74% of patients implanted with high-frequency stimulation systems experienced greater than 50% relief from their back and leg pain as well as improvements in activity levels and analgesic usage.<sup>7</sup> However, this was an open-label trial potentially suffering from the biases that accompany this type of study design. At least one randomized blinded study failed to demonstrate benefit of 5 kHz stimulation on low back and leg pain.<sup>8</sup> Although having better quality clinical trials that will presumably inform us about the clinical utility of high-frequency spinal cord stimulation, there has existed

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◆ This Editorial View accompanies the following article: Shechter R, Yang F, Xu Q, Cheong Y-K, He S-Q, Sdrulla A, Carteret AF, Wacnik PW, Dong X, Meyer RA, Raja SN, Guan Y: Conventional and kilohertz-frequency spinal cord stimulation produces intensity- and frequency-dependent inhibition of mechanical hypersensitivity in a rat model of neuropathic pain. ANESTHESIOLOGY 2013; 119:422–32.

to this time a conspicuous lack of published information providing a clear physiological rationale for this approach. Although the effects of frequency of current used for electroacupuncture and transcutaneous electrical nerve stimulation has been studied in various animal models, relatively little has been published concerning spinal cord stimulation frequency *versus* analgesia until the work of Shechter *et al.*

The experimental paradigm used a standard rat model of neuropathic pain, the spinal nerve ligation model. Small epidural electrodes were implanted in the rats to provide stimulation between 50 Hz and 10 kHz, and a number of behavioral and electrophysiological measurements were made to facilitate comparisons between sensory stimulation, motor stimulation, neural wind-up, and analgesic effects. Reading the report is not for the faint of heart. Although many readers may believe that they are able to interpret basic rodent pharmacology-based studies, the use of electrophysiological as well as behavioral outcomes and the need to compare responses with multiple stimulation protocols across time might be difficult to interpret for many. However, this is a landmark study in many respects. Few other published reports attempt to address as thoughtfully the mechanisms underlying one of our most advanced therapies for chronic pain.

So what did we learn? Among the many findings, perhaps two merit special comment. The first is that each of the high-frequency stimulation protocols (1 and 10 kHz) caused reductions in mechanical allodynia on the first day of stimulation, whereas conventional 50 Hz stimulation provided analgesia not beginning until the second day despite the intensity of stimulation being similar. Furthermore, 1 kHz stimulation provided more intense analgesia and required less intense stimulation to see any effect. Complementing and helping to provide a mechanism for these observations, 1 kHz stimulation also reduced action potentials in  $A\alpha/\beta$  fibers. Although encouraging for high-frequency stimulation, the authors were careful to point out that their experiments were only a few days in duration, and the translation of rat to human stimulation strengths is far from straightforward. Moreover, the exact mechanism for the inhibition caused by high-frequency stimulation remains unclear. The second perhaps key observation was that the C-fiber component of wide dynamic range neuronal wind-up was reduced by 50 Hz but not higher frequency stimulation. The

inhibition of wide dynamic range neurons is widely felt to be at least one of the mechanisms relevant to spinal cord stimulation-mediated analgesia and has been explored previously in an animal model.<sup>9</sup> For many of us, the electrophysiological details may be less relevant than the basic conclusion that different frequencies of stimulation may have different levels of benefit in different clinical settings involving different pain syndromes. These results suggest that adding the capability of using 1 kHz and perhaps higher stimulation may provide an important new tool in our efforts to control chronic pain using spinal cord stimulation.

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