An Overview on Pulsed Radiofrequency Therapy

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Abstract:

A number of electromagnetic field-based technologies are available for therapeutic medical applications. These therapies can be broken down into different categories based on technical parameters employed and type of clinical application. Pulsed radio frequency energy (PRFE) therapy is a non invasive, electromagnetic field-based therapeutic that is based on delivery of pulsed, shortwave radio frequency energy in the 13–27.12 MHz carrier frequency range, and designed for local application to a target tissue without the intended generation of deep heat. It has been studied for use in a number of clinical applications, including as a palliative treatment for both postoperative and non postoperative pain and edema, as well as in wound healing applications. This review provides an introduction to the therapy, a summary of clinical efficacy studies using the therapy in specific applications, and an overview of treatment-related safety.

Keywords: Pain, Radio frequency, PRF.

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Introduction:

Pulsed radiofrequency (PRF) is a novel therapeutic modality with many potential applications in pain management. A variation of conventional continuous radiofrequency (CRF), which has been in use since the mid-1970s, PRF offers the advantage of pain control without the tissue destruction and painful sequelae associated with CRF. This theoretical benefit of PRF is especially alluring in cases of neuropathic pain in which CRF is relatively contraindicated **(Byrd and Mackey, 2008).**

Although Cosman and his associates built the first CRF lesion generator in the early 1950s, CRF was first used to treat pain in 1974. In the early years, technological constraints limited CRF therapy to cervical and lumbar facet disease. However, the introduction of the 22-gauge RF cannula in 1981 allowed clinicians to administer CRF in precise anatomical locations and to control lesion

size. Since that time, CRF has been used to treat a host of painful conditions ranging from lumbar radicular pain to intercostal neuralgia and cervicogenic headaches. Unfortunately, a significant hindrance to the greater acceptance of CRF has been the risk of motor deficits and deafferentation syndrome (**Ahadian, 2004).**

PRF was developed, in part, as a less destructive alternative to CRF. The impetus to conduct research into PRF emerged from an Austrian conference in 1995; Ayrapetyan, a scientist from Armenia, proposed that the clinical effect of CRF might be secondary to magnetic field exposure rather than tissue destruction. Subsequent theoretical work by Cosman showed that the magnetic field produced by CRF was most likely too weak to have a biological effect, but that the rapidly changing electrical field was perhaps significant enough to do so (**Cosman, 2005**).

Later discussions by **Cosman et al. (1998**) centered on the notion that PRF, in theory, was capable of delivering radiofrequency energy sufficient to modulate the electrical field, but insufficient to cause tissue thermocoagulation. Several months after the initial conference, Radionics engineered a prototype PRF generator. Sluijter used this machine in early 1996 to conduct preliminary clinical trials and wrote the first report of the clinical effects of PRF on dorsal root ganglia in 1998.

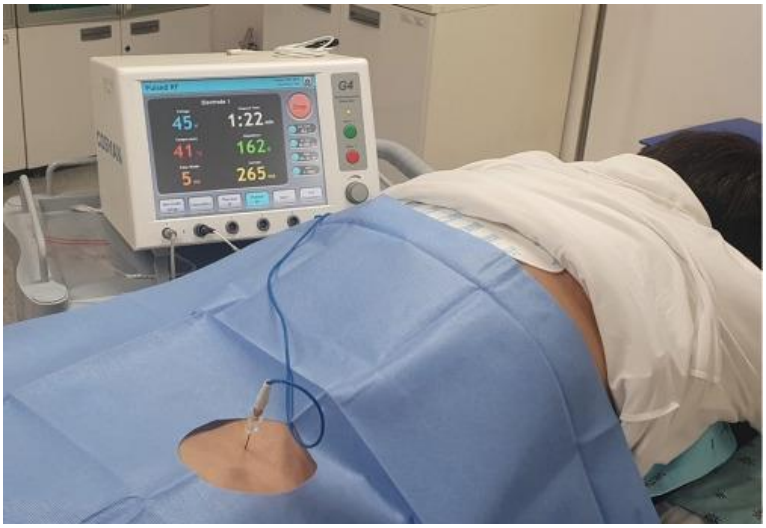

Fig. 1. The application of pulsed radiofrequency procedure on the lumbar dorsal root ganglion (**Park and Chang, 2022).**

Mechanism of Action

Basic theory of action of pulsed radiofrequency

CRF supplies high-frequency continuous current to the targeted nerves. The tip of the probe during the CRF procedure is at approximately 80°C and induces coagulative necrosis to target nerve structures around the probe tip. Because the high temperature of a targeted structure decreases rapidly with distance from the electrode tip, lesions caused by the CRF procedure are well-circumscribed **(Vatansever et al., 2008).**

Therefore, other than damage to the targeted area, other tissues are rarely affected. Electrical neurolysis using CRF can inhibit the transfer of pain signals and has been proven to have a pain-reducing effect in various musculoskeletal disorders. However, neurolysis can result in various side effects, such as sensory deficits, neuropathic pain, and skin burns (**Conger et al., 2020**).

In contrast, PRF uses a radiofrequency current comprising alternatively repeated electrical stimulation with a short duration (e.g., 20 ms) and resting phase (e.g., 480 ms) (Fig. 2). This allows time for heat elimination and maintains the temperature of the target tissue below 42°C. Temperatures below 42°C rarely induce nerve tissue damage. Therefore, adverse effects that can develop after the C-reactive protein procedure do not occur after the PRF procedure. PRF stimulation produces selective long-term depression (LTD) in C-fiber–mediated spinal sensitization (**Boudier-Revéret et al., 2020).**

LTD reduces the efficacy of neuronal synapses in C-fibers, and consequently, inhibits pain signaling from the peripheral nerve to the central nervous system (**Huang et al., 2017**). LTD after PRF stimulation was supposed to be the main pain-reducing mechanism by **Sluijter et al. (1998),** who invented the PRF procedure. Subsequently, several animal studies have been conducted to determine the pain-reducing mechanism of PRF, and these studies demonstrated that several mechanisms other than LTD are associated with pain reduction after the application of PRF (Table 1).

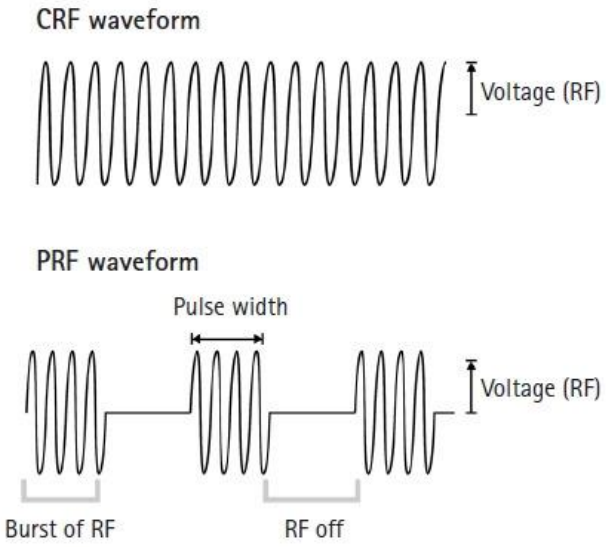

Fig. 2. The waveforms of continuous RF (CRF) and pulsed RF (PRF). While CRF is applied continuously without any resting phase, PRF has a long resting phase between brief electrical stimulation. RF, radiofrequency; Voltage, the amplitude of pulsed RF current (**Park and Chang, 2022).**

Table 1. The suggested pain-reducing mechanism of pulsed radiofrequency (Park and Chang, 2022).

Long-term depression of pain signaling
Changes at the molecular level
Deactivation of microglia at the level of the spinal dorsal horn
Reduction of proinflammatory cytokines
Increment of endogenous opioid precursor messenger ribonucleic acid
Changes in neuronal activity
Enhancement of noradrenergic and serotonergic descending pain inhibitory pathway
Suppression of excitation of C-afferent fibers
Microscopic damage of nociceptive C- and A-delta fibers

Pain-reducing mechanism of pulsed radiofrequency

1. Changes at the molecular level

1) Decrease of microglial activity

Microglia in the dorsal horn of the spinal cord play an important role in the induction and maintenance of neuroinflammation, resulting in chronic neuropathic pain. Activated microglia release various inflammatory cytokines and chemokines that facilitate nociceptive processing at all levels of the neuraxis, including the spinal cord and supraspinal centers. Some previous animal studies have demonstrated the downregulation of microglia in rats with neuropathic pain after the application of PRF **(Cho et al., 2016).**

Cho et al. (2013) applied PRF stimulation (voltage, 45 V; pulse rate, 2 Hz; duration, 2 minutes) to the single dorsal root ganglion (DRG) in 23 Sprague-Dawley rats with sciatica due to herniated discs. After PRF application, mechanical withdrawal thresholds significantly increased, which persisted for 40 days. At 41 days after PRF application, microglia in the spinal dorsal horn were found to be deactivated. **Cho et al. (2016)** applied caudal epidural PRF (pulse rate, 5 Hz; pulse width, 5 ms; duration, 10 minutes) to 35 Sprague-Dawley rats with sciatica due to herniated discs. At 14 days post-PRF, in the sections of the spinal cord from L3, L4, L5, L6, and S1, microglial activation was attenuated in rats with herniated discs. The deactivation of microglia in the spinal dorsal horn after PRF application seems to prevent the progression from acute pain to chronic pain.

2) Reduction of proinflammatory cytokines

Inflammation is associated with acute and chronic neuropathic pain. An increase in proinflammatory cytokines, such as various types of interleukin (IL) and tumor necrosis factor-alpha (TNF-α), has been observed in the DRG and spinal dorsal horn in animal models of neuropathic pain **(Hung et al., 2017).**

Vallejo et al. (2013) evaluated the effect of PRF (voltage, 45 V; pulse width, 20 ms; duration, 3 minutes) on the ipsilateral L5 DRG in six rats exhibiting sciatic nerve injury. Following PRF therapy,

increased proinflammatory gene expression, such as IL-6 and TNF-α, observed in the sciatic nerve and DRG of rats, returned to baseline values. Along with the decreased activation of proinflammatory gene expression, mechanical allodynia in the hind paw was alleviated. **Jiang et al. (2019)** applied PRF (pulse width, 20 ms; pulse rate, 2 Hz; duration, 2 minutes) on the ipsilateral L5 DRG or sciatic nerve in 20 rats with chronic constriction injury to the sciatic nerve. Mechanical allodynia and thermal hyperalgesia were relieved by PRF application. In addition, the authors found that IL-1β and TNF-α in the peripheral blood were downregulated. This anti-inflammatory effect of PRF appears to result in a reduction of various types of neuromuscular pain.

3) Increase in the levels of endogenous opioid precursor messenger RNA and the corresponding opioid peptide

Moffett et al. (2012) investigated the molecular changes after applying PRF using cultured human dermal fibroblasts and human epidermal keratinocytes. After the application of PRF, the levels of endogenous opioid precursor messenger RNA (mRNA; proenkephalin, proopiomelanocortin, and prodynorphin) and corresponding opioid peptides were increased. This finding suggests that PRF exerts an analgesic effect by increasing endogenous opioid precursor mRNA levels.

2. Changes in neuronal activity

1) Activation of pain-inhibitory mechanism

Previous animal studies have demonstrated that the noradrenergic descending inhibitory pathway plays an important role in analgesic action. In addition, activation of serotonin receptors, such as 5-HT1, 5-HT2, and 5-HT3, induces analgesic effects (**Diniz et al., 2015).**

Hagiwara et al. (2009) performed an animal study in rats to evaluate the mechanism of PRF action. They induced unilateral hind paw hyperalgesia by injecting 0.15 mL of Freund's complete adjuvant and applied PRF at 37°C or 42°C for 3 minutes on the sciatic nerves. The pain-reducing effect of PRF was significantly inhibited by intrathecal injection of the alpha2-adrenoceptor antagonist (yohimbine), the selective 5-HT3 serotonin receptor antagonist (MDL72222), and the nonselective serotonin receptor antagonist (methysergide). Based on their results, they suggested that the pain-reducing effect of PRF is correlated with the enhancement of the noradrenergic and serotonergic descending pain inhibitory pathways.

2) Inhibition of the excitatory nociceptive C-fibers

Huang et al. (2017) conducted experiments in rats with neuropathic pain induced by left L5 spinal nerve ligation. After PRF stimulation (pulse rate, 2 Hz; pulse width, 25 ms; duration, 5 minutes) on the left L5 DRG, the excitation of A- and C-afferent fibers was measured by checking the A- and C-components on the evoked field potential recordings. They found that PRF significantly suppressed the C-component overtime after 30 minutes, and this suppression was sustained for at least 140 minutes after PRF. However, the A component was not significantly suppressed after PRF stimulation. Mechanical allodynia and thermal analgesia significantly reduced after 10 and 14 days, respectively.

This result indicates that PRF reduces neuropathic pain by inhibiting or suppressing the excitation of nociceptive C-fibers.

3. Anatomical changes

1) Microscopic damage of the nociceptive nerve

PRF is known to control pain without causing damage to the targeted tissue because the temperature of the targeted tissue does not exceed 42°C during PRF stimulation, and the threshold of tissue destruction is known to range from 45°C to 50°C. However, **Erdine et al. (2009)** reported tissue destruction after PRF stimulation. **Erdine et al. (2009)** conducted PRF stimulation (voltage, 45 V; pulse rate, 2 Hz; pulse width, 1 ms) of the sciatic nerve of rats. The temperature was not allowed to exceed 42°C. The authors evaluated microscopic alterations in the nerve tissue using electron microscopy. After the application of PRF, the destruction of membranes, mitochondria, microfilaments, and microtubules was observed in the C-fibers, A-delta, and A-beta fibers. C- and A-delta fibers are nociceptive nerve fibers. The damage to these fibers was attributed to pain reduction after PRF stimulation.

Clinical Applications

Axial pain

A retrospective study by **Mikeladze et al. (2003)** of 114 patients with cervical or lumbar facet joint pain responsive to diagnostic medial branch blocks and subsequently treated with PRF at 42° C for 120 seconds found that 68 patients had significant pain relief (> 50% pain reduction) that lasted an average of nearly 4 months. They did not find any correlation between treatment efficacy and previous surgery, sex, duration of pain, stimulation thresholds, or spinal level.

Lindner et al. (2006) performed a retrospective analysis of 48 patients with low back pain treated with PRF at 42° C for 120 seconds after reporting pain relief with one series of diagnostic medial branch blocks. The authors found a successful outcome (> 60% improvement) at 4 months in 21 of 29 patients without a history of back surgery and 5 of 19 patients who had undergone surgery, demonstrating not only a significant PRF effect ($P < 0.0001$ and 0.0036, respectively) in each group, but also a significant difference in PRF efficacy between the groups ($P = 0.0028$).

Tekin et al. (2007) conducted a randomized, double-blind, sham lesion study comparing the efficacy of PRF at 42° C for 120 seconds versus CRF at 80° C for 90 seconds in treating lumbar facet pain in 60 patients ($n = 20$ in each group) and found that both CRF and PRF were more effective than local anesthetic alone, but that the duration of pain relief with PRF was less prolonged than that seen with CRF. However, the authors admit that the major limitation to their study was the risk of false-positive blocks.

A somewhat different study was performed by **Teixeira and Sluijter (2006)**; it included eight patients treated with intradiscal PRF who reported a history of axial low back pain presumed to be discogenic in origin, as determined by negative diagnostic medial branch blocks. There was a significant decrease in pain scores after 3 months ($P < 0.0001$). Three patients were subsequently lost

to long-term follow-up, which ranged from 6 to 25 months, but four of five patients available for evaluation indicated that they were pain free. The authors used PRF for 20 minutes at 60 V with a mean tip temperature of 41° C.

Radicular pain

Van Zundert et al. (2007) recently reported a double-blind, sham-controlled, randomized clinical trial of the effects of PRF of dorsal root ganglia in 23 patients with chronic cervical radicular pain. PRF was performed for 120 seconds. The sham intervention involved placement of radiofrequency cannulas as well as sensory and motor testing, but no passing of RF current. At 3 months, the PRF group demonstrated significant benefit in both global perceived effect and visual analogue scale (VAS) measures (P = 0.03 and P = 0.02, respectively). No significant difference was noted between the groups at 3 months with respect to pain medication reduction, the third outcome measure; this measure reached statistical significance at 6 months. The authors conclude that PRF appears to provide pain relief in carefully selected patients with cervical radicular pain, but that this claim needs to be investigated in larger study populations.

Facial pain

Van Zundert et al. (2003) reported results from their study of five patients with idiopathic trigeminal neuralgia treated with PRF at 42° C for 120 seconds. Three of five patients demonstrated complete pain relief at long-term follow-up, ranging from 10 to 20 months. One patient had 90% pain relief at 22 months. The final patient indicated 75% pain relief at 1 month but eventually elected to undergo microvascular decompression.

Navani et al. (2006) reported a single case of PRF of the greater occipital nerve for treatment of occipital neuralgia. The patient, a 62-year-old woman, had a 42-year history of left suboccipital pain. After a positive response to two diagnostic blocks, three rounds of PRF at 42° C for 120 seconds were performed on the medial branches of the C1 and C2 dorsal rami. At a 4-month follow-up, the patient had 60% to 70% pain relief and elected to undergo further PRF, which provided an additional 5 months of relief.

Inguinal pain and orchialgia

PRF has also shown some utility in treating inguinal pain. **Rozen and Ahn (2006)** reported a case series of five patients with chronic ilioinguinal neuralgia after inguinal herniorrhaphy. After a positive response to selective nerve root blocks, each patient was treated with PRF at 42° C for 120 seconds at the T12, L1, and L2 sensory ganglia. Four of the five patients demonstrated significant pain relief at 4 and 9 months. These data are similar to those reported by other pain management practitioners.

In addition, **Cohen and Foster (2003)** reported three cases of patients with groin pain or orchialgia treated with PRF. Each patient underwent PRF of the appropriate nerve (ilioinguinal or genitofemoral) at 42° C for 120 seconds subsequent to receiving diagnostic nerve blocks. All three patients had complete resolution of their pain complaints at 6 months.

Miscellaneous pain syndromes

Vallejo et al. (2006) reported a prospective case series of 22 patients with sacroiliac joint pain treated with PRF who failed to respond to sacroiliac joint injections with steroid and local anesthetic. PRF at 42° C for 120 seconds was performed twice at the L4 and L5 medial branches as well as the S1 and S2 lateral branches. VAS scores were significantly decreased ($P < 0.0001$) at 6 months. Physical well-being and functional well-being measures also showed significantly reduced scores at 6 months (both P values < 0.0001).

A case report presented by **Shah and Racz (2003)** indicated excellent pain relief with PRF of the suprascapular nerve in a patient with glenohumeral osteoarthritis and adhesive capsulitis. PRF was performed at 42° C for three cycles of 120 seconds. Each PRF session afforded the patient with 4 to 5 months of pain relief and improvement in shoulder function.

A retrospective analysis conducted by **Cohen et al. (2006)** of 46 patients with post-surgical thoracic pain found that PRF of the dorsal root ganglion was more beneficial than pharmacologic treatment or PRF of the intercostal nerves. Success was defined as more than 50% pain relief at 6 weeks and 3 months, as well as positive responses to satisfaction and functional improvement questionnaires. No differences between the groups were statistically significant at 6 weeks. At 3 months, however, the group treated with PRF of the dorsal root ganglion had significantly better pain relief than the group treated with PRF of the intercostal nerves ($P = 0.01$). When compared with the medical management group, the dorsal root ganglion cohort demonstrated a pain relief advantage that approached significance ($P = 0.06$). The authors emphasized the need for prospective studies to confirm their findings.

Shabat et al. (2006) performed a prospective cohort study of 28 patients with "neuropathic spinal pain" treated with PRF. PRF was administered at the dorsal root ganglia using electrodes at 42° C for 120 seconds. At 1-month follow-up, 24 of 28 (86%) patients reported complete, moderate, or good pain relief. At 3, 6, and 12 months, some degree of pain relief was reported in 23 of 28 (82%), 20 of 28 (71%), and 19 of 28 (68%) patients, respectively. The authors did not conduct a statistical analysis of their data.

PRF technique

There are currently few studies on the use of PRF in patients with persistent Spinal Pain Syndrome (PSPS) type 2, and almost always the series almost always include several etiologies other than PSPS type 2. Most of these reports use needle electrodes for the transforaminal route. Among the patients, >50% pain relief was found at follow-up in 45%, 40%, and 33% (**Turkyilmaz, 2022).**

Three of these studies reported few cases of PSPS type 2. The use of an epidural catheter has been described in three studies. In a clinical series of only PSPS type 2 long-term (from 3 to 6 months follow-up) pain success varied from 32% to 48% of a series with pain caused by various pathologies; in the patients of Gulduren Aydin et al. the technique proved to be statistically effective both in patients with PSPS type 2 and in other diseases. In all these studies the cathode was the skin plate and

the anode the cannula with active tip electrode or the epidural catheter tip **(Gulduren Aydin et al., 2021).**

Patients with lumbosacral radicular pain were subjected to PRF using two catheter needles with active tips less than 1 cm apart. This technique was proposed to improve clinical results and this objective was achieved in the randomized controlled trial. However no patients had PSPS type 2, which was indeed an exclusion criterion **(Chang et al., 2007).**

Compared with monopolar PRF, it has been suggested that bipolar PRF would produce a denser and larger electrical field with better results on lumbosacral radiculopathy. Whith a monopolar current output the covered area is 12.8 mm × 7.8 mm, while the covered area of the bipolar PRF should be 15.5 mm × 11.8 mm thus bipolar PRF can cover the Dorsal Root Ganglion (DRG) more sufficiently. However with this technique the area of administration of the current does not cover the entire ganglion unlike the new technique we describe below which for anatomical and current administration reasons covers the entire ganglion **(Lee et al., 2018).**

The setting of the treatments in the various series is usually 120 s with 45 volts at temperature of 42° using the cannula needle, while in cases treated with the epidural electrode the voltage varies from 65 to 80 volts for 240 s. The described follow-up varies from 1 month to 3 years **(Gulduren Aydin et al., 2021).**

When the conventional monopolar technique is used such fields are found in a spherical zone around the active tip of the electrode, and a distance of approximately 2–3 cm is reached when 45 V are applied. Control of this distribution of electricity on the DRG is not always possible: in fact the distance D1 is not sufficient to cover the area of the entire ganglion (Figure 3) **(Dario and Capelli, 2023).**

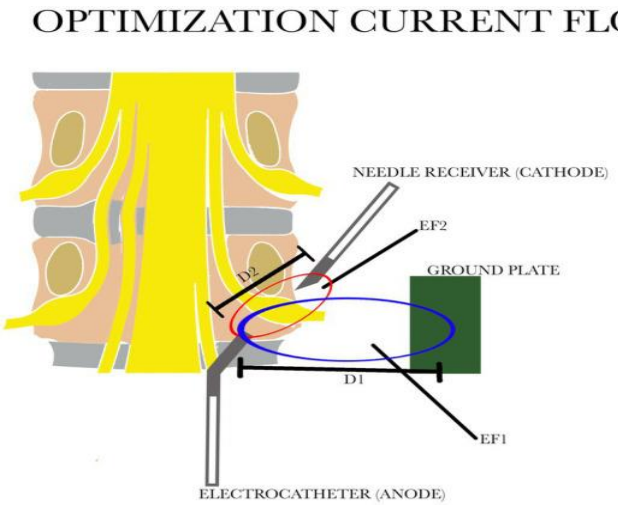

Figure 3: Comparison of the two electric fields: in blue EF1 with the distance between the electrocatheter and the ground plate D1; in red EF 2 with the distance between the electrocatheter and the needle receiver D2. D1 is greater than D2. EF, electric field **(Dario and Capelli, 2023).**

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