

## Radiofrequency therapy in back pain and complex regional pain syndrome

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### Abstract

Percutaneous radiofrequency procedures are frequently used in the management of chronic pain. Continuous radiofrequency (CRF) has been established as a safe and effective treatment for pain originating from facet and sacroiliac joints through the coagulation of their nerve supply. Different methods have been proposed to account for the complex nerve supply of the sacroiliac joint. Due to its neurodestructive property, CRF was limited to the treatment of neuropathic pain. When applied to the dorsal root ganglion (DRG) for spinal pain or to the sympathetic ganglia in treatment of complex regional pain syndrome (CRPS), heat-related side effects have been reported. With the development of pulsed radiofrequency (PRF), a less destructive alternative to CRF became available which is more suitable for treating neuropathic pain. In the treatment of several pain conditions PRF was applied with varying success rates. The results with PRF adjacent to the DRG are promising; whereas for facet and sacroiliac joint pain, PRF could not yet be proven to be equally effective as CRF. As for PRF in CRPS, there is almost no evidence available. The potential of PRF seems to lie in those areas where CRF is of limited value. On the other hand, it is questionable whether PRF will ever be equally effective in indications where the application of CRF is already well established. Neither has PRF nor its mode of action been validated so far, despite of the active use of PRF in clinical practice. The amount of literature in both cases is increasing; however, further studies are still urgently needed.

### Introduction

The percutaneous radiofrequency neurolysis of the dorsal primary rami was first introduced by Shealy in 1975 as a treatment for pain stemming from the facet joints and as a less traumatic alternative to surgical denervation.<sup>1</sup> Since then, the new technique has been increasingly refined and employed in the treat-

ment of facet joint pain<sup>2</sup> and sacroiliac joint syndrome<sup>3</sup> as well as in the modulation of the dorsal root ganglion (DRG) to relieve radicular pain.<sup>4</sup> This is not surprising considering the lack of a validated conservative management strategy for the given pain conditions.<sup>5</sup> The frequently performed intraarticular injection of steroids, notably for facet joint pain, has been proved ineffective<sup>6,7</sup> and, in rare cases, even turns out to be the cause of severe complications.<sup>8-10</sup> The thermal or so-called continuous - radiofrequency (CRF) produces a well-controlled and circumscribed lesion; thus, making it a safe and atraumatic procedure.<sup>11,12</sup> However, facts such as the coagulation of the target tissue and reported heat-related side effects when placed adjacent to the DRG<sup>13,14</sup> contraindicated the use of thermal radiofrequency to treat neuropathic pain syndromes.<sup>15</sup>

This changed when Slappendel found CRF of 67° or 40°C adjacent to the DRG to be equally effective<sup>14</sup> thus, questioning a heat lesion as the underlying mechanism of action. Subsequently, Sluijter developed the pulsed radiofrequency (PRF)<sup>16</sup> as an alternative and less destructive radiofrequency method suitable for the treatment of neuropathic pain conditions.<sup>17</sup> Since PRF proved to have a remarkable safety margin and is easier to perform than CRF, it was very quickly introduced in the treatment of various pain conditions including sacroiliac joint pain, facet arthropathy, post-surgical pain, radicular pain and general neuropathic pain conditions. Nonetheless, the research concerning the biological effects of PRF considerably lagged behind its clinical use.<sup>15,18</sup> The first histopathologic studies<sup>19</sup> were published four to five years after its introduction as a treatment.<sup>16</sup> Knowledge about the mode of action and evidence on its effectiveness have ever since been increasing.<sup>20</sup>

This review aims at providing an overview of the use and the effectiveness of CRF and PRF in the treatment of chronic back pain and CRPS as well as of the current understanding of the mechanism underlying the analgesic effects of radiofrequency procedures.

### Mode of action

#### Thermal RF

The aim of a thermal radiofrequency procedure (CRF) is to create a well-circumscribed coagulative necrosis in the target tissue.<sup>11,12</sup> A radiofrequency needle, which is placed on the target structure and a large ground plate placed on the skin, are connected to a generator. The tissue of the body closes the circuit. An alternating current in the radiofrequency range generates high-frequency electrical fields which induce an oscillation of charged molecules in the tissue. This molecular oscilla-

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tion produces heat, thereby coagulating the tissue within a few millimeters around the electrode. The temperature achieved on the surface of the electrode, usually 80°C to 85°C, depends on the amplitude of the applied current and diminishes rapidly with increasing distance from the electrode.<sup>18,21,22</sup>

#### Pulsed RF

In contrast to thermal (continuous) radiofrequency, a high-voltage radiofrequency current is delivered in short pulses of 20 ms. The relatively long silent phase between the bursts allows the heat to dissipate.<sup>18,21</sup> In this way, using the same voltage used in CRF, the tissue temperature can be kept at 42°C, which is below the neurodestructive temperature of 45°C. On the other hand, PRF can produce far stronger electric fields.<sup>23</sup> The commonly used protocol suggests a pulse duration of 20 ms at a frequency of 2 Hz.<sup>18,20</sup>

The mechanism responsible for the effectiveness of the pulsed radiofrequency is not yet completely understood. The fact that the electrode temperature is kept at 42°C, which does not produce a thermal injury like CRF, lead to the hypothesis that the effects of PRF are temperature independent.<sup>21,24</sup> Histopathologic studies only show the appearance of early ultra structural changes, such as axonal changes with abnormal membranes and morphology of mitochondria, disorganization of microfila-

ments and microtubules,<sup>25</sup> reversible endoneurial edema, fibroblast activation with collagen deposition<sup>11</sup> and separation in myelin configuration.<sup>24</sup> Some authors postulate that the electric fields and the high transmembrane potentials they induce are the underlying mechanisms of many of the effects of PRF.<sup>20,23</sup> Indeed, high electric fields are able to affect neural membranes and cause electroporation.<sup>26</sup> In addition, the lower electric fields are believed to cause neuromodulation and alterations in synaptic transmission.<sup>20,27</sup> Moreover, low frequency stimulation of primary afferents is able to induce long-term depression (LTD) of synaptic transmission in the spinal cord.<sup>19,23,28,29</sup> The LTD can have a relevant effect on antinociception because it antagonizes the long-term potentiation that is believed to play an important role in the transmission and integration of sensory information in chronic pain syndromes.<sup>20,23,28-30</sup> The upregulation of the transcription factors c-Fos<sup>31,32</sup> and ATF3 (activating transcription factor 3)<sup>33</sup> in the dorsal horn of the spinal cord after exposure of dorsal roots to PRF is a further indicator that the sensory fibers have been activated by the electric fields. Nevertheless, the actual role of these transcription factors in the analgesic effects of PRF remains unclear.<sup>18,20,21</sup> However, ATF3 was selectively upregulated in small and medium caliber DRG neurons<sup>33</sup> which indicates that PRF selectively targets small unmyelinated C and slightly myelinated A $\delta$  nociceptive fibers.<sup>15</sup> The analgesia is also more pronounced and enduring when administered to the DRG rather than to a peripheral nerve.<sup>11,33</sup> In animal studies PRF was found to relieve neuropathic pain.<sup>34,35</sup> Hyperalgesia and neuropathic pain, induced through ligation of the sciatic nerve, could be alleviated by the application of PRF to the L5 and L6 dorsal roots.<sup>34</sup> Furthermore, the PRF treatment of the sciatic nerve inhibited hyperalgesia in adjuvant induced inflammatory pain. Interestingly, the effect could be attenuated by intrathecal application of anti-adrenergic drugs. This hints an inclusion and enhancement of the noradrenergic and serotonergic descending pain inhibitory pathways that underlie the analgesic effect of PRF.<sup>35</sup> Briefly, such as Chua and colleagues stated as they got to the heart of the mode of action: *PRF appears to have genuine biological effects in cell morphology, synaptic transmission and pain signaling, which are likely to be temperature independent.*<sup>20</sup>

## Radiofrequency treatment in back pain

### Facet joint syndrome

Pain stemming from facet joints is an important source of chronic low back pain and

is mostly associated with degenerative processes of the spinal column.<sup>36,37</sup> The prevalence of facet joint mediated pain based on controlled diagnostic blocks in patients with chronic back pain ranges from 15% to 45% in the lumbar region, to 36% to 67% in the cervical spine and 34% to 48% in the thoracic region.<sup>38,39</sup> The connection between each spinal level consists of paired, posterolaterally situated, true synovial facet joints and the intervertebral disc which form a sort of three-joint complex.<sup>37</sup> Each facet joint is innervated by the medial branch at the same level and from one level above the joint. The medial branch of the posterior primary ramus crosses the neck of the superior articular process of the segment below, and then runs into the groove formed by the junction of the root of the superior articular and the transverse process. At the L5 level, it is the dorsal ramus that lies in the groove between the superior articular process of the sacrum and the ala, before the medial branch arises.<sup>40-42</sup>

The diagnosis of z-joint pain cannot be made on the basis of physical or radiological findings! Both proved inept for the distinction between patients with facet joint pain and those with another cause of back pain.<sup>43-46</sup> Some clinical features used as a screening instrument, may increase the probability that facet arthropathy is present.<sup>47,48</sup> However, the only validated method to reliably diagnose facet joint pain is a clinically controlled protocol of local anesthetic blocks of the supplying medial branches.<sup>38,49</sup> Under fluoroscopic guidance and aided by X-ray contrast, in order to prevent aberrant spread of the local anesthetic or venous uptake,<sup>50</sup> the medial branches of the suspected joints are anesthetized on two different occasions, once with a long and once with a short-acting local anesthetic. Only if considerable pain relief occurs following each block, and only if the duration of the relief is consistent with the known period of effectiveness of the respective anesthetic, the block can be considered as true-positive.<sup>51-53</sup> The cut-off value for a successful block is usually set at 50% pain relief,<sup>54</sup> whereas other authors recommend at least 80%,<sup>55,56</sup> 90%<sup>51</sup> or even total pain relief.<sup>52</sup> Yet, the research concerning this debate suggests that there is no difference in the outcome of the radiofrequency neurotomy if 50% or 80% of pain relief is used as a cut-off value.<sup>47,54</sup> Too stringent selection criteria, in addition to the considerable false negative rate of diagnostic blocks, may even exclude suitable patients from a potentially effective treatment.<sup>52,54,57</sup> Single blocks are not sufficient due to their high false-positive rates.<sup>51,54</sup>

After careful patient selection with comparative blocks, the supplying medial branches are coagulated with CRF, usually at 80°C for 90 s, to interrupt the pain signaling from the symptomatic facet joints.<sup>56</sup> Under radiological

guidance the electrodes are inserted from caudal and placed at the base of the superior articular process at its junction with the transverse process, where the medial branch passes by.<sup>58,59</sup> The maximum extent of tissue coagulation occurs with decreasing distance of isotherms along the non-insulated tip of the electrode.<sup>18,23,60</sup> For this reason the electrode should lie parallel and within 2 mm of the target nerve for maximum coagulation. This is not the case with perpendicular electrode placement. In addition, multiple lesions should be produced along the course of the nerve in consideration of anatomical variations.<sup>58,59</sup> The lengths of the lesion correlates with the time of repair of the nervous tissue and thus with the duration of pain relief.<sup>61</sup> When pulsed radio-frequency is used, the electrode should lie perpendicular to the nerve.<sup>18</sup> The strong electric fields, that are believed to be the major mechanism of action, reach the greatest intensity distal to the electrode tip.<sup>23</sup>

### Cervical region

For the cervical region, some well-designed studies using appropriate diagnostic criteria and techniques are available. The only randomized, placebo-controlled, double-blind trial (RCT) of Lord *et al.* randomly assigned 24 patients with chronic cervical pain after whiplash injury to radiofrequency neurotomy or sham treatment. Very stringent diagnostic criteria were applied with complete relief to placebo-controlled blocks or no relief when saline was injected. The electrodes were placed parallel to the correct target point and 2 to 3 lesions were produced at slightly different locations for each nerve. At 27 weeks, 7 out of 12 patients in the treatment group were absolutely pain-free. The median time before pain returned to 50% of the preoperative level was 263 days (37.5 weeks) in the treatment group, versus 8 days in the placebo group.<sup>62</sup> An observational<sup>63</sup> and a prospective study<sup>64</sup> using a similar diagnostic and technical protocol as Lord *et al.*<sup>62</sup> but conducted in a routine clinical setting show comparable results. In the former, 75% of the patients were pain-free after 35 weeks (245 days).<sup>63</sup> In the latter, 71% of 28 patients were completely relieved for at least 90 days. The median time until pain returned to the 50%-level was 219 days for all patients and even 422 days considering only the successful cases (71%).<sup>64</sup> In both studies, similar pain relief was achieved by repeating the procedure.<sup>63,64</sup> A study comparing the results on 46 litigant and nonlitigant patients, with the aim of detecting a potential secondary gain, did not find a significant difference between the groups. The mean pain reduction on VAS amounted to 4.6 points after 1 year.<sup>65</sup> In a further study, 19 of 28 patients (68%) showed 75% or more pain reduction at 6 months.<sup>66</sup> A very recent prospective evaluation in a private com-

munity setting including a total of 379 patients was again able to show successful outcomes. Diagnosis and radiofrequency treatment were performed strictly after the recommended guidelines in the cervical, thoracic, lumbar and sacroiliac region over a period of 9 years. Seventy-six percent of 151 patients treated on the cervical level were considered to have a successful outcome, which was defined by a minimum of 50% pain reduction for at least 2 months. Among the patients recorded during the follow-up between 6 and 36 months, 78% reported an average pain relief of 88% for a mean duration of 12 months.<sup>67</sup>

#### Thoracic region

For the thoracic region, very sparse evidence is available from only two retrospective and one prospective study. Forty patients with chronic thoracic spinal pain, who failed to respond to conservative treatment, received a radiofrequency neurotomy of the medial branch. After two months, 48% of the patients were pain-free and 35% were relieved of more than 50% of the pain. During the mean follow-up time of 31 months, these proportions stayed in the same range: 44% of the patients with complete and 39% with more than 50% relief.<sup>68</sup> In the trial of Tzaan *et al.*, 15 procedures were performed on the thoracic level. The successful outcome was delineated at a minimum of 50% of pain relief. Forty percent of the patients showed a successful outcome over an average follow-up period of 5.6 months.<sup>69</sup> Recently, the above mentioned prospective study showed that 68% of the patients had at least 50% pain relief for a minimum duration of 2 months. Of the persons that joined the follow-up, 75% reported an average pain relief of 85% for a mean duration of 9 months.<sup>67</sup>

#### Lumbar region

There are some RCTs for radiofrequency neurotomy in the lumbar region showing inconsistent evidence. Van Kleef found a significant difference between the treatment and the control group regarding the reduction in pain VAS, global perceived effect and functional disability at 8 weeks after treatment. In a 12-month period, the number of success patients, defined as a 2-point reduction in VAS, was significantly higher in the radiofrequency group.<sup>2</sup> Leclaire failed to provide positive results in his study. No significant treatment effect was apparent at 12 weeks.<sup>70</sup> In the largest RCT so far, van Wijk allocated 81 patients to radiofrequency ablation or sham treatment. The combined outcome measure (including VAS, physical activities and analgesic intake) showed no difference between groups at 3 months, just as all the other secondary outcome parameters. Only the general perceived effect (more than 50% pain relief) improved significantly after the radiofrequency treatment. Interestingly, both groups had significant pain relief (VAS)

that lasted until the 12-month follow-up.<sup>71</sup>

It is noteworthy that all of the above mentioned RCTs have some remarkable diagnostic and technical flaws which may influence their findings.<sup>72,73</sup> All of them used single diagnostic blocks that have a high false positive rate.<sup>2,70,71</sup> The inclusion criteria in the study of Leclaire consisted of pain relief for at least 24 hours in the week after the intraarticular injection of a mixture of corticosteroids and local anesthetics.<sup>70</sup> This non-validated and quite odd diagnostic method may have led to the inclusion of a great number of false-positive patients, thus making their findings largely invalid. In two studies the electrode was placed perpendicular to the nerve<sup>2,70</sup> and the produced lesion might have been too small.<sup>58,60</sup> Furthermore, Leclaire does not describe the exact anatomical position of the electrode,<sup>70</sup> whereas van Kleef and van Wijk performed only one lesion per nerve.<sup>2,71</sup> It is however recommended to produce several lesions in view of possible variations in the course of the medial branch.<sup>59</sup>

The first study in the lumbar region using comparative diagnostic blocks and accurate technique is non-randomized, but shows more convincing results. Out of 15 patients, 60% had at least 90% pain relief and 87% experienced 60% of relief after 12 months. The extent of the pain reduction was also reflected in a significant improvement of functional and disability scores.<sup>74</sup> With a much larger patient population treated in a routine clinical setting, Gofeld *et al.* succeeded in reproducing these results. Among the 174 patients, 119 (68.4%) reported good (more than 50%) to excellent (more than 80%) pain relief lasting for a period of 6 to 12 months. In 36 patients the analgesic effect continued even for 12 to 24 months.<sup>75</sup>

These positive outcomes were confirmed in the newest RCT with 40 patients. It is the only randomized study that uses an accurate diagnostic procedure with controlled diagnostic medial branch blocks and correct surgical technique. In the active treatment group, a significant improvement was documented in back and leg pain, generalized pain, back and hip movement, quality of life and global perception of improvement at 6 months. All these variables were significantly greater in the radiofrequency group compared to the placebo group. Unfortunately, the follow-up was not extended over 6 months.<sup>76</sup> In the above mentioned prospective evaluation of Speldewinde, 69% of the patients that were contactable for the follow-up (151) reported an average pain relief of 85% during a mean duration of 11 months. Overall, 69% of 180 patients had at least 50% pain relief for a minimum of 2 months.<sup>67</sup> Some smaller studies show varying but positive results, with long lasting pain relief for over one year for some of the patients<sup>77,78</sup> as well as significant functional improvement.<sup>78,79</sup>

The effect of a medial branch neurotomy has the tendency to wane, typically between 6 and 12 months, when the nerve regenerates. However, the pain relief may be reinstated with similar duration and success by repeating the procedure.<sup>80</sup>

#### Pulsed radiofrequency for facet joint pain

There are some attempts to apply pulsed instead of thermal radiofrequency to the medial branch, mainly in the lumbar region. This was first described in a trial with 114 patients with chronic lumbar and cervical facet joint pain. Sixty-eight patients (60%) experienced more than 50% of pain relief with an average duration of 3.9 months.<sup>81</sup> Similar results were produced in a retrospective analysis. Twenty-five of 47 patients (53%) experienced a pain reduction of at least 60% at 4 months.<sup>82</sup> These first trials gave rise to two RCTs.<sup>83,84</sup> One compared the outcomes in a CRF, a PRF and a sham treatment group. At 6 months the pain relief and functional improvement were comparable between the groups. Nonetheless, no effect could be seen any longer in the PRF-group after 1 year. The number of satisfied patients and the number of those not using analgesics was higher with CRF treatment.<sup>83</sup> In the second RCT, the difference of improvement in VAS and disability scores between PRF and CRF group did not reach significance at 3 months. On the other hand, the relative change of the same variables over time within the groups were significant when CRF - but not when PRF - was applied.<sup>84</sup> Both authors concluded that PRF has a comparable short-term outcome to CRF, but that the effect of the latter lasts longer.<sup>83,84</sup>

In summary, radiofrequency therapy for facet joint pain is a promising treatment option, but there is still insufficient evidence to draw a definitive conclusion about its effectiveness. The main reasons for this circumstance are the lack of high quality RCTs and the inconsistency in diagnostic, technical and evaluation criteria across the studies.<sup>85</sup> Particularly in the lumbar region, most of the RCTs fail to clarify its efficacy<sup>2,70,71</sup> due to some substantial technical and methodological flaws.<sup>73</sup> Some systematic reviews do not take these into account and consequently postulate only limited evidence for RF-denervation.<sup>86,87</sup> However, their efficacy might be underestimated.<sup>56</sup>

Newer reviews include trials which are non-randomized for the most part but performed following proper guidelines.<sup>49,88</sup> Datta concludes that RF-neurotomy in the lumbar region has moderate evidence but a strong level of recommendation, due to the fact that the benefits clearly compensate the risks and the morbidity.<sup>49</sup> In the review of Boswell, the efficacy of RF-therapy is considered moderate in the cervical and lumbar spine.<sup>88</sup> However, the level of

evidence increases considerably if only the well-designed studies of the cervical region, which follow a protocol of producing multiple lesions, are taken into consideration.<sup>62-64</sup> Regarding the thoracic region, the evidence is uncertain due to the sparse literature available in the field.<sup>88</sup> Nevertheless, some newer results suggest that RF-therapy could be equally effective.<sup>67</sup>

The aim of the introduction of pulsed radiofrequency for the same indications was to reduce the heat-related side effects. In addition, the procedure is easier to perform and less time-consuming. The literature available to date is not able to clarify the effectiveness of the PRF, but points to the fact that it is less efficient than CRF for this indication, particularly considering the long-term outcomes.<sup>20</sup>

Finally, the RF-neurotomy of the medial branch is the only available, effective treatment option for facet joint pain when conservative treatment has failed.<sup>61</sup> It can be performed in an outpatient setting, has a low complication rate<sup>89</sup> and provides a pain relief of up to one year in a substantial part of patients, if the accurate technique is used.<sup>67,75,76</sup> When pain returns, the effect can be reinstated equally successful by repeating the procedure.<sup>63,64,67,80</sup>

### Sacroiliac joint syndrome

In about 10% to 38% of patient with low back pain, the sacroiliac joint is the major source.<sup>90</sup> Similar to facet joint pain, this condition is difficult to diagnose, because the clinical features overlap with the ones of pain caused by other structures. The standard diagnostic tools are intraarticular joint blocks performed under fluoroscopic guidance aided by the spread of X-ray contrast in order to guarantee a correct needle placement and intraarticular spread of the local anesthetic.<sup>91</sup> There is no consensus on the use of controlled diagnostic blocks. In view of the false-positive rate of 20% to 54% of the single injections,<sup>90</sup> some authors recommend a double-block protocol.<sup>90,92-94</sup> However, to date no difference in the outcome for different diagnostic block protocols could be found.<sup>95</sup> Due to the complex anatomy of the sacroiliac joint, Dreyfuss affirmed that the so-called comparative multi-site, multi-depth lateral branch blocks should be used to better prevent false-negative responses.<sup>96</sup> A combination of provocative tests increases the probability for SI-joint pain.<sup>91,97</sup> Radiological imaging is of little value for the diagnosis.<sup>94</sup> The complex innervation of the SI-joint is still controversial and apparently very variable among individuals. Some postulate a predominant innervation from lateral branches of the sacral and L5 dorsal ramus<sup>98,99</sup> whereas others describe an additional supply from ventral rami and the sacral plexus.<sup>100</sup> The lateral branches exit at the lateral aspect of the dorsal sacral foramina with a

great variability in number and course, forming a sort of arcade of small nerve fibers anastomosing with dorsal rami around the foramina.<sup>101</sup> For this reason, the production of multiple lesions per site is recommended.<sup>91</sup> To overcome the complex innervation, different radiofrequency techniques have been developed.

Gevarez performed 3 conventional CRF lesions under CT-guidance in the posterior interosseous sacroiliac ligament and an additional one targeting the L5 primary dorsal ramus. Out of 38 patients, 34% were free of pain and 32% reported substantial pain reduction at 3 months on a 4-point scale.<sup>102</sup>

In a study of Cohen et al. 9 patients underwent a RF-denervation of the L4-L5 primary dorsal rami and the S1-S3 lateral branches. After the insertion of the electrode, electrical stimulation was used in order to correctly locate the target nerves before a single lesion at 80° was produced. Eighty-nine percent of the patients experienced more than 50% of pain relief during 9 months.<sup>103</sup> With a similar technique, Yin achieved more than 50% of pain reduction in 64% of the patients and complete relief in 36% of the cases, at the 6 months follow-up. In contrast to Cohen, the L4 dorsal ramus was not lesioned.<sup>101</sup>

In a retrospective trial over 33 patients, Ferrante created multiple intraarticular lesions with a bipolar system.<sup>3</sup> With this method, the ground plate on the skin is replaced by a second electrode that is positioned close to the other, allowing the current to flow between them and to create a more extended lesion than with the conventional CRF.<sup>104</sup> Only 36% of the patients had at least 50% of pain relief at 6 months, but that effect lasted until 12 months.<sup>3</sup> Burnham slightly modified Ferrante's technique by applying multiple bipolar strip lesions to the lateral borders of the dorsal sacral foramina. The L5 dorsal ramus was coagulated in the usual manner. The median reduction of the pain intensity was of 4.1 points (NRS). The pain alleviation was significant during 12 months, but diminished from 6 months onwards.<sup>105</sup>

Three studies used internally water-cooled electrodes to increase the size of the lesion. By cooling the electrode's surface, the temperature is maintained at 60°C and the tissue next to the electrode is not charred. Tissue charring usually limits the extent of coagulation by ionic oscillation. All procedures produced several lesions adjacent to the lateral aspect of dorsal sacral foramina. In addition, the L5 dorsal ramus was lesioned in the usual manner with a normal radiofrequency electrode.<sup>106-108</sup> A retrospective trial analyzed 26 patients after 3 to 4 months. The responders (50%) had a mean pain reduction of 71% (-5.2 points in VAS) and a significant improvement in disability scores. The decrease in pain scores was of

39% (-2.8 points) if the non-responders were taken into consideration as well.<sup>106</sup> The only existing RCT for RF-treatment of SI-joint pain, reports more than 50% of pain relief in 64% of the patients at 3 months and in 57% at 6 months after the procedure. In addition there was a significant functional improvement. In the placebo group no treatment effect could be seen at 3 and 6 months.<sup>107</sup> A very recent observational study was able to show promising results with this technique in 15 patients. The mean pain reduction consisted of 75% and 63% at 3 and 6 months respectively, linked to a significant improvement in disability scores.<sup>108</sup>

Vallejo is the only one who applied PRF to the sacral lateral branches and L4-L5 dorsal primary rami in 22 patients who failed to respond to two therapeutic SI-joint injections. Seventy-three percent of the patients had good (>50% reduction) to excellent (>80% reduction) pain relief for more than 3 months.<sup>109</sup>

Due to the fact that the diagnostic and outcome evaluation criteria as well as the applied technique are widely varying across the studies, it is difficult to determine the effectiveness of radiofrequency treatment for SI-joint pain. A systematic review shows limited evidence (after AHRQ-criteria) for long and short-term relief.<sup>90</sup> However, in absence of other treatment options for patients who do not respond to conservative management or therapeutic SI-joint injections, CRF is recommended as the only effective alternative.<sup>90,91</sup> The best technique to overcome the complicated anatomy still needs to be determined. However, the cooled probe technology seems to provide better outcomes. On the other hand, studies directly comparing conventional and cooled radiofrequency are still lacking.<sup>95</sup>

### Dorsal root ganglion

CRF treatment of the dorsal root ganglion (RF-DRG) was first described by van Kleef *et al.* as an alternative method to treat chronic cervical pain. The idea was to inhibit nociceptive stimuli that are conducted through the DRG.<sup>4,13</sup> The electrode was placed adjacent to the dorsal aspect of the ganglion, and the temperature was kept at 67°C in order not to completely damage the neural tissue and to reduce the risk of complications.<sup>18</sup>

In a RCT, van Kleef compared RF-DRG to sham-treatment in 20 patients with chronic cervicobrachialgia. At 8 weeks post-treatment, a successful outcome ( $\geq 2$  reduction in VAS) was recorded in significantly more patients in the treatment group (89%) than in the placebo-group (18%).<sup>13</sup> Contrary to this, a further RCT with 80 patients was not able to identify a difference between a RF-DRG at 67°C and a sham-treatment after 3 months.<sup>110</sup> Interestingly, Slappendel found RF-DRG at 67°C and 40°C to be equally effective. Both groups achieved a significant reduction of pain

at 3 months without significant difference between the groups.<sup>14</sup> This promoted the idea that not the heat-lesion but rather the RF-current itself could be the underlying mechanism of action. This subsequently led to the development of PRF,<sup>18</sup> first introduced by Sluijter.<sup>16</sup>

The side effects of CRF such as transient neuritis, loss of muscle strength and deafferentation pain<sup>13,14</sup> can be avoided with PRF.<sup>2,17</sup> A case series provided preliminary evidence in patients with intractable neuropathic pain, who achieved lasting relief after PRF without any side effects.<sup>17</sup> In a further study, 68% of 28 patients with neuropathic spinal pain reported significant pain relief at 12 months. Two patients were pain-free, 6 experienced more than 50% and 11 more than 30% of pain relief.<sup>111</sup> Cohen concludes in a retrospective trial that PRF of the DRG is more effective than pharmacotherapy or PRF of the intercostal nerves in 49 patients with postsurgical thoracic pain. At 3 months follow-up, 54% in the DRG-group reported significant pain relief (>50%) compared to only 7% in the ICN and 20% in the conservative treatment group.<sup>112</sup> In the RCT evaluating PRF, 23 patients with cervicobrachialgia were allocated to either PRF of the DRG or sham-treatment. Eighty-two percent of the patients and 33% of the control subjects had significantly better outcomes in global perceived effect (> 50% improvement) at 3 months. In regard to pain reduction (20 points in VAS), the proportion of successful cases was 82% in the treatment versus 25% in the sham-group. At 6 months, the analgesic intake was significantly reduced in the treatment group, whereas the pain relief and the global perceived effect just failed to reach significance.<sup>113</sup> A previously conducted study by the same authors showed similar results.<sup>114</sup>

There is one trial that exclusively treats patients with lumbar radicular pain. Seventy-six patients were randomly allocated to only PRF or PRF followed by CRF at 54°C adjacent to the DRG. At 2 months, 70% in the PRF-group compared to 82% in the group additionally treated with CRF showed a significant pain reduction (2 point reduction in NRS). The mean duration of the pain relief was 3.18 months versus 4.4 months with combined treatment and loss of any analgesic effect at 8 months. The authors conclude that adding a thermal lesion does not offer a significant benefit.<sup>115</sup>

RF-DRG provides a significant pain relief in many patients with neuropathic spinal pain that is often unresponsive to conservative treatment.<sup>20</sup> CRF and PRF seem to have comparable efficacy, even if one randomized trial shows no benefit with CRF treatment.<sup>110</sup> PRF should be preferred, because it is safer and the heat-related side effects can be avoided.<sup>116</sup> While the results in the cervical region are promising, the evidence in the lumbosacral

region is very sparse. Only two studies provide inconsistent outcomes.<sup>110,115</sup> Nevertheless, the trial using PRF with positive results<sup>115</sup> suggests that this procedure applied in the lumbar region may achieve a similar benefit. In any case, further studies are needed to provide evidence in these questions.

### Radiofrequency treatment of CRPS

The IASP (International Association for the Study of Pain) describes CRPS as follows: *A term describing a variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event often resulting in significant impairment of motor function, and showing variable progression over time.* CRPS usually occurs after limb trauma or surgery, and a distinction is made between Type 1 without, and Type 2 with definable nerve lesion. The affected area is typically not limited to the original extent of the injury.<sup>117</sup> The diagnosis is principally made on the basis of history and symptoms, which consist of continuous pain, allodynia and hyperalgesia, skin temperature asymmetries, skin color changes, edema, abnormal sudomotor activity and trophic changes of hair and nails. Furthermore, there are signs of motor dysfunction such as a decrease in the range of motion, weakness, tremor, dystonia and involuntary movements. The symptoms appear in various combinations and may change over time.<sup>117-119</sup>

The complex pathophysiology is still not completely clarified. Multiple peripheral and central pathomechanisms are involved which maintain each other in terms of a vicious circle.<sup>120,121</sup> One mechanism is hypoxia, which may be induced by impaired microcirculation and vasoconstriction caused by endothelial dysfunction with altered ratio of the vasoactive substances NO and ET-1.<sup>120,122</sup> There is evidence for sterile<sup>122</sup> as well as for neurogenic inflammation.<sup>123</sup> The degeneration and dysfunction of distal small fiber axons may underlie denervation supersensitivity through inappropriate firing.<sup>124,125</sup> The permanent nociceptive input may cause central sensitization and cortical reorganization of sensory and motor units. In addition, disturbed efferent motor pathways possibly lead to the signs of motor dysfunction. Secondary psychological phenomena, like fear of pain resulting in movement anxiety, are mentioned as a further mechanism.<sup>121</sup>

Finally, the sympathetic nervous system is believed to play an important role in pain generation and to possibly influence the peripheral blood flow and sweating abnormalities. Through chronic inflammation or nerve lesion, chemical coupling between sympathetic and nociceptive neurons in skin may occur.

Additional upregulation and sensitization of  $\alpha$ -adrenoceptors associated with the nociceptive fibers may lead to hypersensitivity to sympathetic outflow.<sup>126</sup> Stimuli provoking increased central sympathetic activity (startle stimulus, forehead cooling)<sup>127</sup> and intradermal injection of noradrenalin can provoke pain in CRPS patients.<sup>128</sup> The component of pain, that is maintained by circulating catecholamines or sympathetic efferent innervation and that may be mitigated by sympathetic blocks, is considered as sympathetically maintained pain (SMP). SMP is associated with various pain disorders<sup>117</sup> and appears in about 50% of the patients with CRPS.<sup>120,127</sup>

Repetitive sympathetic blocks with local anesthetics are widely used to treat SMP in CRPS in the upper<sup>128-130</sup> and lower limb<sup>130-132</sup> with mostly positive short-term outcomes. In order to achieve longer lasting pain relief, sympathectomy with phenol or CRF has been proposed. The presence of SMP should be identified with sympathetic blocks prior to the neurolytic procedure.<sup>119</sup> A 50% or greater relief to diagnostic block was found to be highly correlated with functional improvement at long-term follow-up after sympathectomy.<sup>133</sup>

There are two retrospective studies evaluating radiofrequency lesion of the stellate ganglion (SG). In the first study 86 patients with different chronic pain syndromes were treated. 40.7% of the patients had more than 50% of pain relief. In 27 patients that were available for follow-up, the analgesic effect lasted for an average of 52.4 weeks. Compared with the results of other methods of SG blockade in the literature, radiofrequency was found to be equally effective.<sup>134</sup> In the second study, 28 patients with SMP of the upper extremity received a total of 37 operations. Ninety-three percent of the procedures resulted in an „excellent and lasting sympathectomy that continued for over 1 year in 63%.<sup>135</sup> A lumbar sympathetic block with radiofrequency (RF-LSB) is described in 20 patients. Twenty-five percent had a complete relief and 45% a partial pain release that lasted from 1 week and up to 3 years in certain patients.<sup>136</sup> There are two studies comparing radiofrequency to phenol sympathectomy.<sup>137,138</sup> One study demonstrates better outcomes with phenol. After 8 weeks, 89% in the phenol group versus only 12% in the RF-group showed signs of sympathectomy. However, only phenol caused post-sympathectomy neuralgia.<sup>137</sup> A RCT assigned 20 blinded patients to either phenol or radiofrequency sympathectomy. A statistically significant reduction in various pain scores was seen in each group during the 4-month follow-up. But again, in the phenol group one case of post-sympathectomy neuralgia occurred.<sup>138</sup> A case report describes the outcome of LSB with PRF in a patient with severe CRPS after spinal surgery. Pain and hyperalgesia decreased from 95 to 25

(-73.6%) in VAS and the pathologic alterations of the tissue and the circulation disappeared after 3 days. The clinical effect lasted until the 4-month follow-up.<sup>139</sup> In a retrospective analysis of 12 patients with CRPS treated with PRF of the sympathetic ganglia, 58% experienced good to excellent results at the 3-month follow-up.<sup>140</sup>

Despite the frequent application in clinical practice, the use of CRF sympatholysis is based on very little high-quality evidence.<sup>141</sup> There is only one RCT comparing phenol and radio-frequency neurolysis,<sup>138</sup> and it was never investigated against placebo. Phenol neurolysis achieves slightly better outcomes but is also associated with a higher risk of complications like deafferentation pain.<sup>137,138</sup> In addition, soluble neurolytic agents are more likely to damage other neural structures through inadvertent spread.<sup>142</sup> Hence, radiofrequency should be preferred.<sup>119</sup> Surprisingly there are only two case reports describing PRF for this indication,<sup>139,140</sup> despite its frequent use in clinical practice. The non-destructive nature of PRF makes it more favorable to treat neuropathic pain conditions and eliminates the risk of deafferentation syndrome.<sup>140,142</sup>

In general the studies contain very small patient samples. Nevertheless, radiofrequency sympathetic blocks seem to be an effective treatment in many patients who had a positive response to diagnostic blocks. It is advocated once conservative treatment has failed<sup>119</sup> and should be administered as early as possible.<sup>129,143</sup> The achieved analgesic effect can facilitate the restoration of function of the limb by physiotherapeutic methods.<sup>142</sup> Sympathetic blocks may also lead to the resolution of other pathologic changes, which is an indication for the complex connections between the different pathomechanisms in CRPS.<sup>144</sup>

## Conclusions

CRF and PRF seem to be attractive treatment options in carefully selected patients with chronic pain who failed to respond to conservative management and to whom no other effective alternative can be offered to provide satisfactory pain relief. It constitutes a safe procedure with low morbidity that can be performed in an outpatient setting. Moreover, its analgesic effect can be reinstated by repeating the procedure.<sup>63,64,67,80</sup> CRF is an effective treatment for the pain of facet joint and sacroiliac joint origin. Some technically incorrect RCTs discredited CRF in the treatment of facet arthropathy. Nevertheless, good evidence is available from well-designed prospective studies<sup>72,88</sup> and more recent reports with larger patient samples.<sup>67</sup> These studies demonstrated that significant pain relief can be provided to a

majority of patients when using the accurate technique. PRF was found to be less effective than CRF in the treatment of facet joint pain.<sup>83,84</sup> As for sacroiliac joint pain, the best technique to deal with the complex innervation pattern still needs to be evaluated. When applied to the DRG in the treatment of radicular pain, the utility of CRF is limited. Due to its neurodestructive properties, side effects are more frequent.<sup>84,115,116</sup> However, compared to CRF, slightly better results with simultaneously less complications have been achieved with the use of PRF to the DRG.<sup>113,115</sup> In the treatment of CRPS, the use of CRF was found to be equally effective but safer than chemical sympatholysis.<sup>137,138</sup> Despite the frequent utilization of PRF for sympatholysis, there is almost no literature available. Generally, the potential of this less destructive method seems to lie in the areas where CRF is of limited value, namely in neuropathic pain conditions like radicular pain or CRPS. On the other hand, it is questionable if PRF will ever be equally effective in treatments where CRF is already well established, such as the thermo coagulation of the medial branch.<sup>20</sup> Chua and colleagues<sup>20</sup> note that sometimes may an insufficient *dose* of PRF-current is applied. An animal study found the antialloodynic effect to be significantly greater when the duration of PRF exposure was increased from 2 to 6 min.<sup>145</sup> Despite its active use in clinical practice, PRF is not validated yet nor is its mode of action.<sup>15</sup> The literature in both cases is accumulating and will hopefully clarify the role of PRF in interventional pain management. In many fields, further studies based on more uniform criteria are urgently needed.

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