

Case Report: Effects of Systolic Extinction Therapy in a Patient with Seropositive Rheumatoid Arthritis

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SINGLE CASE STUDY

TREATMENT DESIGN. In conjunction with pharmacotherapy (PT), systolic extinction training (SET), which combines operant behavioral pain therapy (OBT) and cardiac-gated electrical baroreceptor training, was carried out 4 hours a week for 5 weeks. OBT modifies the learned association between social influences and pain [5], observed as enhanced pain behavior and subjective pain severity in response to solicitous spouse behaviors. The treatment goal is reduction of pain behaviors, lower subjective pain reports, and increased frequency of healthy adaptive behaviors, such as goal-oriented adaptive physical activities, increased assertiveness in social relationships, and reduced catastrophizing.

Baroreceptor training delivers pain-free and painful stimuli synchronized with the cardiac cycle, which reactivates the diminished BRS. Individuals with a hypertensive reactivity to prolonged stress may develop permanently increased blood pressure with reduced variability that diminishes activity of arterial baroreceptors. Diminished BRS is associated with increased pain in patients with chronic pain. Cardiac-gated baroreceptor training increases blood pressure variability with resultant activation of the BRS and inhibition of sympathetic cardiomotor and vasoconstrictor neurons by reactivation of dmNTS reflex arcs responsible for the regulation of blood pressure, pain, anxiety and sleep.

CLINICAL OUTCOME. After 5 weeks of SET in combination with MTX, Sulfasalazine and cortisone, the patient's **clinical pain** was reduced from 70 to 0 (VAS= 0-100) and she became pain free for 27 weeks. At 12-month follow-up, she reported a (0-100) pain intensity of 15 for RA and 0 for FM & OA, at the 27 months follow-up 10 for RA and OA,) for FM whereby the **cortisone was reduced** from 20mg to 5 mg maintained for the following 27months (Figure 1). The patient has gotten 2 refreshment sessions during the follow-up. **Blood pressure became normotensive** (92/53 mm/Hg at rest and 112/63 mm/Hg during stress) 12 months after therapy and could be maintained for further 24 months (116/67).

Sleep rhythm normalized, with 32 arousals and 2 awake phases in the 2nd half of the night.

BRS increased to 69.1% after SET combined with MTX, Sulfasalazine and cortisone, to 70.34% 12 months and 71.67% 27 months after therapy.

Disease Activity Score (DAS28 with CRP) fell from 5.26 to 2.88 after treatment and remained low ($3.14 \leq 3.2$) at the 27 month-follow-up.

Tender points on examination were no longer detectable. During 27 months, the patient experienced 1 episode of inflammation of the right knee. No further inpatient treatment was necessary.

IMMUNOLOGICAL CHANGES. CRP reduced to 8.7 mg/l after therapy and remained low (14.7 mg/l) 27 months after therapy. IgM and IgG rheumatoid factors were normal at 12 and 27 months. The anti-CCP-antibody reduced to 94.65% and was 81.67% 27 months after SET in combination with MTX, Sulfasalazine and cortisone (Table 1). The pharmacotherapy (MTX and cortisone) decreased the anti CCP-antibodies to 73.89% within the first 3 years before SET was added.

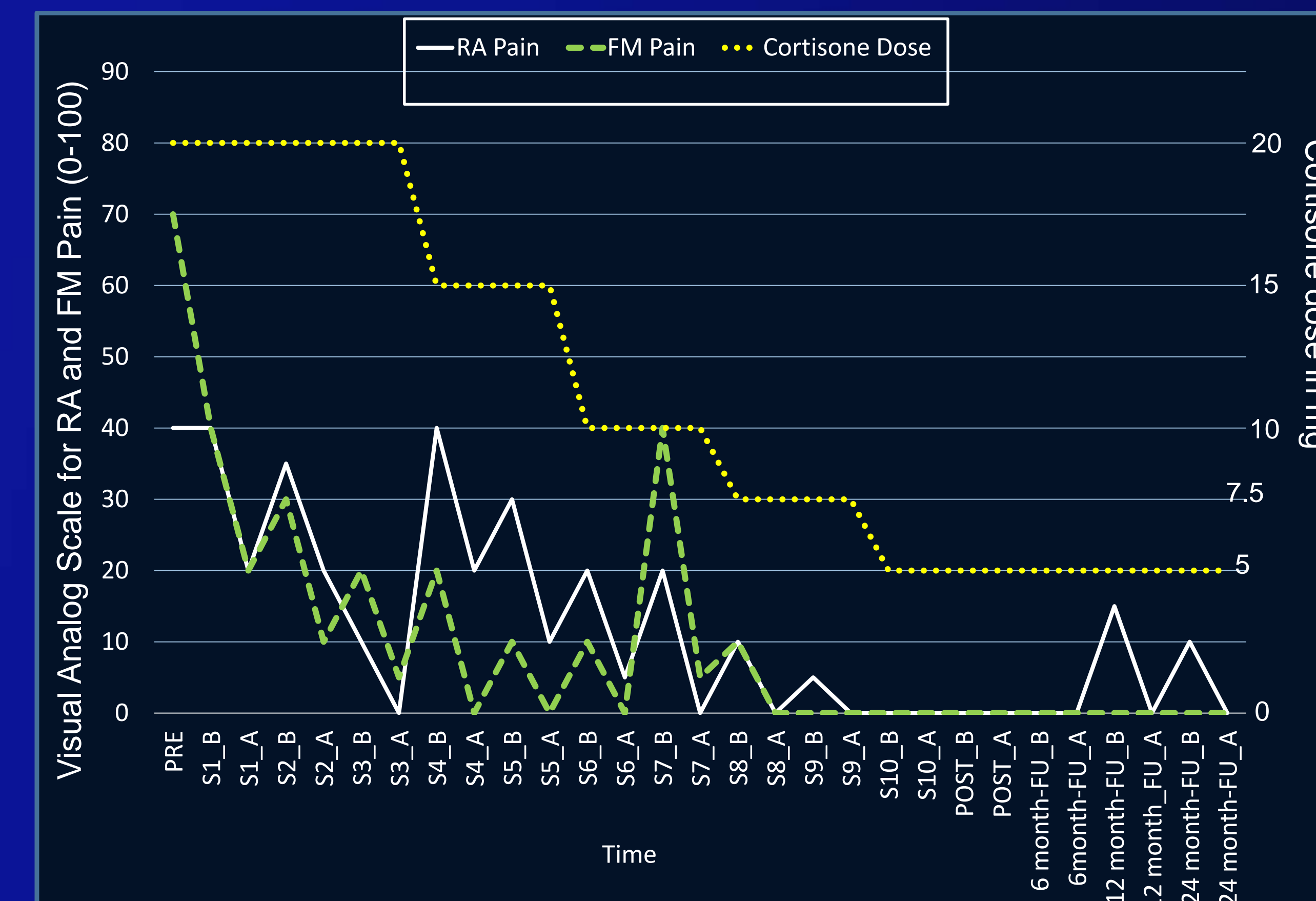


Fig. Clinical pain in RA and FM (dashed) as well as cortisone dose (dotted) before, during, after, 6, 12 and 24 months after SET in combination with PT.

DISCUSSION. It is generally accepted that stimulation of carotid sinus and cardiopulmonary baroreceptor afferents, which are activated by dynamic changes of blood pressure and respiratory rate, reduce pain. Baroreceptors provide signals to the brain stem and the dorsal medial nucleus tractus solitarius (dmNTS). The dmNTS is responsible for inhibition of both pain, anxiety, sleep quality, and blood pressure. In healthy individuals an elevation in resting arterial blood pressure leads to a reduction in acute pain sensitivity. Studies show that in persistent pain conditions the interaction between blood pressure and pain sensitivity is impaired. **Diminished baroreceptor sensitivity**, which is influenced by classical and operant conditioning, may provoke pain chronicity. The permanent stress-related increase of blood pressure leads to a lack of dynamic changes of the pressure in the carotid sinus. In effect, the carotid baroreceptors “**learn**” not to react anymore. The NTS no longer receives inhibitory signals and, therefore does not inhibit pain and anxiety.

Diminished NTS activation leads to the development of pain chronicity in the subgroup of patients who develop hypertension in prolonged stress situations. In addition, **diminished BRS and NTS activation effects the immune system.** Norepinephrine (NE), through stimulation of the β_2 -adrenoreceptor-cAMP-protein Kinase A pathway, inhibit the production of type 1/proinflammatory cytokines, such as interleukin (IL-12), tumor necrosis factor- α , and interferon- γ by antigen presenting cells and T-helper 1 (Th1) cells. Through this mechanism, endogenous catecholamines may cause a selective suppression of Th1 responses.

CONCLUSION. This single case suggests that SET, by restoring BRS and NTS activation, is synergistic with pharmacotherapy in reducing inflammation and/or pain in RA, OA, and fibromyalgia.

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HISTORY. A 66-year-old Caucasian female patient presented to the pain clinic Marburg with a 3-year history of seropositive rheumatoid arthritis (RA) principally manifested as symmetrical pain and swelling in small joints of the hands, wrists, elbows with increased rheumatoid factor (RF =27, Table1), anti-CCP-antibody (443 U/ml, norm:<10 U/ml), elevated CRP (50.1, norm<5.0mg/l) and elevated ESR (38/80 mm). ANA, and antibodies to U1-n-RNP, SS-A, SS-B, and Scl-70 were absent. Radiographic findings consistent with osteoarthritis were evident in hips, knees, hands and feet. Synovitis was evident in small joints of middle and ring fingers of both hands and in both wrists. She was diagnosed as seropositive RA and osteoarthritis (OA). Fibromyalgia (FM, 13 / 18 painful tender points) developed 3 years after the onset of RA. The first three years were characterized by multiple flares and 3 inpatient admissions despite treatment with MTX and corticosteroids (Prednisolone).

The patient was referred to the pain clinic in 2014 where she reported a pain intensity (0-100 VAS) of 40 for RA & OA and 70 for FM. Systolic hypertension (blood pressure 162/75 mm/Hg) was present, increasing to 191/73 mm/Hg during physical stress as measured in a standardized psychophysiological test. Disturbed sleep rhythm was characterized by 354 arousals with 33 transformations into awake state, as well as a diminished baroreflex sensitivity (BRS). The patient had difficulty bending down, lifting, carrying objects weighing >1kg, walking >10 meters, resulting in her having to rest on a couch >10 h/day. Pharmacological treatment included MTX (15mg), Cortisone (20mg), and Sulfasalazine (2000mg), which was added following a 6 month-episode of a high disease activity (DAS28 = 5.26) immediately before SET started.

Lab	11/2010 onset	8/2011 29 m before SET	7/2012 18 m before SET	8/2013 6 m before SET	1/2014 1 m before SET	7/2014 1m after SET	8/2015 15 m after SET	8/2016 27m after SET
CRP (< 5.0 mg/l)	22.0	37.4	49.2	23.4	50.1	8.17	16.1	14.7
RF (< 15 U/ml)	68	52	20.6	2s4.5	27	<15	<15	<15
RhF IgM (<40 U/ml)	na.	na.	na.	82	27	<23	<23	<23
RhF IgA (<20 U/ml)	na.	na.	na.	27	49.1	5.7	5.6	3.9
Anti-CCP-antibody (< 7 U/ml)	433.4	na.	302.6	na.	113.18	23.2	na.	83.8

Table. CRP, Rheumatoid factors and anti-CCP antibody before and after SET in combination with MTX, Sulfasalazine and Cortisone

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