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Case Report

Effects of Systolic Extinction Therapy in a Female Patient with Seropositive Rheumatoid Arthritis. A Case Report

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Abstract

Important components of intrinsic pain regulatory systems are modulated by cardiovascular dynamics that influence bar reflex sensitivity (BRS). Various studies have shown BRS is diminished in chronic pain patients compared to healthy controls. Our own study has shown a 62% increase in BRS after systolic extinction training (SET), a cardiac gated electrical baroreceptor training combined with operant-behaviour therapy. A case report evaluated the effects of SET in a 66-year old patient with rheumatoid arthritis (RA) comorbid with osteoarthritis (OA), fibromyalgia (FM) and hypertension. Clinical pain, BRS, blood pressure, sleep, Disease Activity Score (DAS28), and autoantibodies were assessed before, after and 12 months after the 28-hour-treatment with SET combined with 15mg MTX and 20mg cortisone. The clinical pain was reduced from 70 to 0 (VAS= 0-100) and maintained for 26 weeks. At 12-month follow-up, pain intensity on VAS = 15 for RA, 0 for OA and FM. Blood pressure was normotensive, sleep rhythm normalized, BRS increased to 70.34%, DAS28 changed from 5.26 to 3.11 (≤ 3.2). IgM, IgG Rheumatoid Factors and anti-CCP-antibody had returned to normal values. The results suggest that SET, by restoring BRS activation, is synergistic with pharmacotherapy in reducing inflammation and/or pain in RA, OA and FM.

Keywords: Anti-CCP-Antibody; Baroreflex Sensitivity; DAS28; Late Onset Rheumatoid Arthritis; Rheumatic Factor; SET

Introduction

Rheumatoid arthritis (RA) is a chronic and destructive inflammatory disease characterized especially in the involvement of small joints. RA usually develops in middle-aged adults; however, it may occur at childhood or old age, too [1]. RA is the second most common rheumatic disease after osteoarthritis (OA) but it is the most destructive for synovial joints. RA has a prevalence of 0.5 to 0.8 per 100 adults and an increase in incidence and prevalence with age [2]. Several studies indicate that disease manifestation, severity, progression and prognosis of RA differ in relation to age at disease onset [3]. Patients with late onset RA (onset >65 years) report a higher severity of pain than patients with young onset RA that is related to hypertension [4]. Similar to other chronic pain conditions, the inverse relationship of blood pressure and pain is disturbed: To higher, the blood pressure to higher the pain severity [5]. Blood pressure elevations influence baroreceptors that, in turn, provide input to the dorsal medial nucleus of the solitary tract (dmNTS) reflex arcs (Figure 1) that modulate BP, heart rate (HR), vessel dilation, autonomic balance, sleep, and pain perception [6]. The dmNTS projects via excitatory (glutamatergic) fibers in the ascending reticular activating system (ARAS) to the rostral ventrolateral medulla (RLVM), coordinating multi-phasic autonomic responses throughout the body. The dmNTS modulates brain network regions such as the amygdala and anterior cingulate cortex that are critically involved in pain perception and sleep [7,8]. Several studies report disturbed autonomic function with a diminished bar reflex sensitivity in patients with rheumatoid arthritis [9,10]. Diminished BRS is associated with increased pain in patients with chronic pain [5,11]. A behavioural pain treatment with neuromodulator called “Systolic Extinction Training” (SET) that combines operant behavioural pain therapy (OBT) and cardiac-

gated electrical baroreceptor training could reactivate baroreflex sensitivity and reprogram the brainstem in female patients with fibromyalgia. Long-term effects of 12 months after a 20hours SET showed pain freedom in 82% of the patients [12]. We hypothesize that a patient with an inflammatory rheumatic disease such as rheumatoid arthritis can also reactivate their baroreflex sensitivity and influence pain perception by the behavioural neuromodulator methods such as the SET.

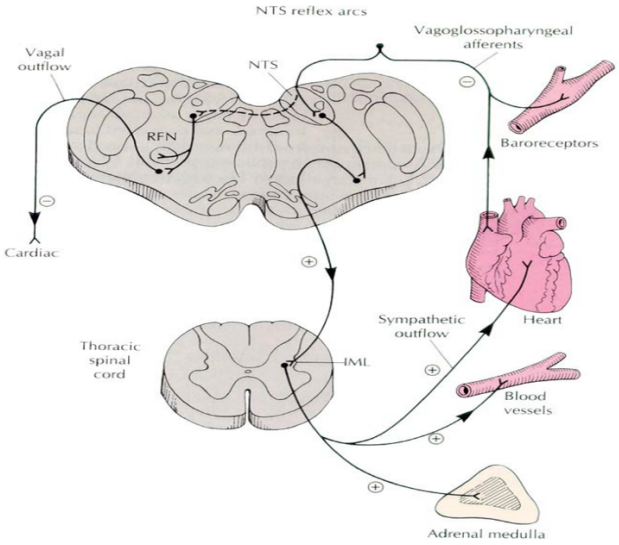

Figure 1: NTS Reflex arcs.

Material and Methods

The study was approved by the local Ethics committee of the Philipps-University Marburg, Germany.

Assessment of the case

A 66-year-old Caucasian female patient presented to the pain clinic Marburg with a 3-year history of seropositive late onset rheumatoid arthritis (RA) principally manifested as symmetrical pain and swelling in small joints of the hands, wrists, elbows with increased rheumatoid factor (RF =27, Table 1), 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. 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, [10]). 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), which was added following a 6 month-episode of a high disease activity (DAS28 = 5.26).

Treatment Design

In conjunction with pharmacotherapy (PT), systolic extinction training (SET), which combines operant behavioural pain therapy (OBT) and personalized baroreceptor training (pBRT), was carried out 4 hours a week for 7 weeks. OBT modifies the learned association between social influences and pain [13], observed as enhanced pain behaviour and subjective pain severity in response to solicitous spouse behaviours. The treatment goal is reduction of pain behaviours, lower subjective pain reports, and increased frequency of healthy behaviours, such as goal-oriented physical activities, increased assertiveness in social relationships, and reduced catastrophizing [14]. A personalized Baroreceptor Training (pBRT) delivers pain-free and painful stimuli synchronized with the cardiac cycle, which reactivates the diminished BRS [15]. Individuals with a hypertensive reactivity to prolonged stress may develop permanently increased blood pressure with reduced variability that diminishes activity of arterial baroreceptors located in the carotid sinus [16]. Cardiac-gated baroreceptor training increases blood pressure variability with resultant activation of the BRS [17] and inhibition of sympathetic cardio motor and vasoconstrictor neurons by reactivation of NTS reflex arcs responsible for the regulation of blood pressure, pain, anxiety and sleep [6]. For SET adherence was assessed by completion of homework assignments.

Results

After 7 weeks of SET in combination with 15mg MTX, 20mg cortisone, the patient's clinical pain was reduced from 70 to 0 (VAS= 0-100) and she became pain free for 26 weeks. At 12-month follow-up, she reported a (0-100) pain intensity of 15 for RA and 0 for FM & OA. Blood pressure became normotensive (92/53 mm/Hg at rest and 112/63 mm/Hg during stress) 12 months after therapy. Sleep rhythm normalized, with 32 arousals and 2 awake phases in the 2nd half of the night. BRS increased to 69.1% immediately after SET combined with MTX and cortisone, and to 70.34% 12 months after therapy. During these 12 months, the patient experienced 1 episode of inflammation of the right knee. No further inpatient treatment was necessary (Figure2). Her Disease Activity Score (DAS28 with CRP) fell from 5.26 to 3.25

immediately after treatment and remained low (3.11 ≤ 3.2) at the 12 month-follow-up. Tender points on examination were no longer detectable.

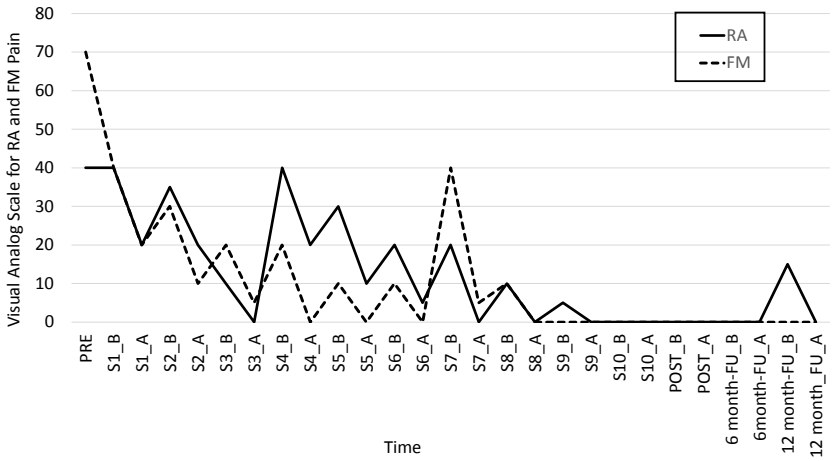

Figure 2: Clinical pain in RA and FM (dashed line) before, during, after, 6 and 12 months after SET in combination with PT. S1_B = Clinical Pain in Session 1 before pBRT stimulation; S1_A = Clinical Pain in Session 1 after pBRT stimulation; FM: Fibromyalgia; PT: Pharmacotherapy, RA: Rheumatoid Arthritis; SET: Systolic Extinction Training.

Immunological Changes

Her CRP reduced to 13.3 mg/l immediately after therapy and remained low (15.5 mg/l) 12 months after therapy. IgM and IgG rheumatoid factors as well as anti-CCP-antibody normalized 12 months after SET (Table 1).

Lab	11/2010 onset	8/2011 29 months before SET	7/2012 18 months before SET	12/2013 1 month before SET	5/2014 1 Month after SET	7/2015 15 months after SET	Normal
RF in U/ml	68	52	20.6	27		7	<15
RhF IgM in U/ml				82		<23	<40
RhF IgA in RE/ml				27		5.6	<20
Anti-CCP-antibody in U/ml	433			433		<5	<10

RF and RhF: Rheumatoid Factor, Anti-CCP-antibody: Anti-cyclic citrullinated peptide antibody

Table 1: Rheumatoid factors before (T1) and 12 months after SET in combination with MTX and cortisone (T3).

Discussion

An emerging body of evidence provides support for an important interaction between pain and cardiorespiratory regulatory systems [5]. It is generally accepted that the stimulation of carotid sinus and cardiopulmonary baroreceptor afferents, which are activated by dynamic changes of blood pressure and respiratory rate, reduce pain. Activated baroreceptors provide signals to the brain stem terminating, in particular, in the nucleus tractus solitaries (NTS, [8]). The NTS is responsible for inhibition of both pain and anxiety in addition to the improvement of sleep and blood pressure. In healthy individuals, there is a functional interaction of the cardiovascular and pain regulatory systems, whereby an elevation in resting arterial blood pressure leads to a reduction in acute pain sensitivity. Activation of carotid sinus and cardiopulmonary afferents attenuates pain. Studies show that in persistent pain conditions the interaction between

blood pressure and pain sensitivity is impaired [18]. Diminished baroreceptor sensitivity, which can be influenced by classical and operant conditioning [19], may provoke pain chronicity [5]. 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 also has an important influence on development of pain chronicity in a subgroup of patients who develop hypertension in prolonged stress situations. In addition, diminished BRS and NTS activation has effects on the immune system [20].

Conclusion

These results suggest 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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Conflict of interest statement: There is no potential conflict of interest.

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