Efficacy of Systolic Extinction Training (SET) in Reducing Pain and Interference in Female Fibromyalgia Patients that Respond to Stress with Elevated Blood Pressure

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Abstract: (words 241)

**Aim**. An intrinsic pain regulatory system is modulated by both cardiovascular dynamics that influence baroreflex sensitivity (BRS) and diminished in Fibromyalgia (FM). Baroreceptors relay cardiovascular output to the dorsal medial nucleus tractus solitarius reflex arcs that regulate pain, sleep, anxiety, and blood pressure. This study evaluated the effects of Systolic Extinction Training (SET) that combines operant treatment (OT) with BaroReflexTraining (BRT). BRT delivers peripheral electrical stimulation immediately after systolic or diastolic peak of the cardiac cycle. This study compared SET to (1) OT-TENS, transcutaneous electrical stimulation *independent* of cardiac cycle, and (2) aerobic exercise (AE)-BRT in FM patients with elevated blood pressure stress responses.

**Method**. Seventy-two female FM patients were randomized to receive either SET (n=21), OT-TENS (n=20), or AE-BRT (n=21). Outcome assessments occurred before (T1), immediately after 5 weeks of treatment (T2), and 6-12-month follow-up (T3).

**Results**. In contrast to OT-TENS and AE-BRT, patients receiving SET reported a significantly greater reduction in pain and interference (all *Ps*<0.01) that were maintained at 6-12-month follow-up. Clinically meaningful pain reduction at T3 was reached in 82% of SET, 39% of OT-TENS, and 14% of AE-BRT treated patients. BRS increased 57% after SET, compared to OT-TENS and AE-BRT (*P*s<0.01).

**Conclusion**: SET resulted in significant and long-lasting pain remission and interference compared to the OT-TENS and AE-BRT suggesting that BRS modification was the primary mechanism. Research with larger samples and other chronic pain conditions appears to be warranted to confirm and extend the results.

**Significance and Innovations**. (words 84)

1. Approximately 50% of female FM patients demonstrate hypersensitive stress reactivity. SET, which combines Operant Treatment (OT) with BaroReflexTraining (BRT), reduced long-term pain and interference in 82% for these patients.
2. OT-TENS showed 38% pain responders and did not reactivate baroreflex sensitivity (BRS).
3. AE (Aerobic Exercise)-BRT showed only 13% pain responders, suggesting that the pain network was not successfully inhibited with this treatment.
4. The clinically significant reduction of pain intensity is associated with the increase of BRS.

**Introduction** (3692 words)

Fibromyalgia (FM) is characterized by chronic pain, sleep, and fatigue. FM has significant heterogeneity in central mechanisms[[1]](#endnote-1), genetic[[2]](#endnote-2), endocrine[[3]](#endnote-3) and autonomic factors. Cardiovascular response patterns (both hypertone and hypotone), sudomotor and muscular reactions[[4]](#endnote-4),[[5]](#endnote-5),[[6]](#endnote-6), and psychological characteristics[[7]](#endnote-7),[[8]](#endnote-8) differ. Patients with hypotone stress response often report only moderate pain, whereas hypertone patients report high levels of pain, interference, anxiety, pain behaviors, and low levels of physical activity[[9]](#endnote-9). Treatment response is similarly variable[[10]](#endnote-10),[[11]](#endnote-11). These heterogeneous responses suggest not only differing mechanisms for the development and maintenance of FM, but also the need for differential treatment.

Operant Therapy (OT) focuses on the development of adaptive behaviors and pain behavior extinction[[12]](#endnote-12). FM patients with extensive pain behaviors, solicitous reinforcing spouses, physical impairment, and frequent physician visits, appear to achieve the greatest benefit from OT[[13]](#endnote-13),[[14]](#endnote-14). OT’s strong effects are accompanied by central changes[[15]](#endnote-15) and the normalization of the cardiovascular pain response suggesting a reactivation of an intrinsic pain regulatory system[[16]](#endnote-16).

Stress and pain have been shown to increase blood pressure (BP) in a subgroup of FM with hypertone stress response6. Increased BP in the carotid activates baroreceptors that relay the cardiac input to the dorsal medial nucleus tractus solitarius (dmNTS, *Figure 1*). The dmNTS regulates pain, sleep, anxiety, BP and projects to other parts of the pain network[[17]](#endnote-17),[[18]](#endnote-18),[[19]](#endnote-19). s

An acute pain stimulus triggers an increase of BP, which increases heart rate triggering an analgesic biochemical response. The efficacy of the heart rate response to BP changes can be measured by baroreflex sensitivity (BRS[[20]](#endnote-20),[[21]](#endnote-21)), a biomarker for health of the dmNTS reflex arcs and the autonomic nervous system17,[[22]](#endnote-22). In pain-free individuals, acute pain produces a sympathetically driven analgesic response that *decreases* BP back to normal levels through parasympathetic activation17,[[23]](#endnote-23).

In contrast, chronic pain patients with hypertensive stress response show increased pain with increased BP6. The pain regulatory system is impaired due to diminished BP variability and NTS reflex arc response18,19, which reduces the intrinsic analgesic response to peripheral noxious input,[[24]](#endnote-24),[[25]](#endnote-25). Long-term stress provokes persistent increased hypertension, a learned diminished BRS, and persistent widespread pain20,[[26]](#endnote-26),[[27]](#endnote-27). Almost one-half (48%) of FM patients demonstrate a dysfunctional BP stress response6,9.

BaroReflexTraining (BRT) stimulation (see below) targets BRS through stimuli delivered after the systolic peak of the cardiac cycle[[28]](#endnote-28). Systolic Extinction Training (SET) combines BRT, which improves BRS with OT which reduces pain behaviors and physical interference.

BRS can also be increased with aerobe exercises (AE)[[29]](#endnote-29). Cardiovascular fitness training is believed to reactivate the diminished BRS as well as to improve metabolism as components of mental and physical relaxation relevant for pain reduction[[30]](#endnote-30). AE has had success as a component of multimodal rehabilitation with FM patients[[31]](#endnote-31).

In the current study, we examined whether SET can restore arterial BRS in female FM patients who present an elevated cardiovascular risk profile (i.e., long-standing diabetes, geriatric age group, hypercholesterolemia, and/or hypertension) and compared to 2 other active treatments (OT-TENS (Transcutaneous Electrical Nerve Stimulation), and AE - BRT). We hypothesized that despite multiple cardiovascular risk factors, SET would increase BRS and thus reduce chronic pain and improve physical functioning compared to other nonpharmacological treatments.

**Specific hypotheses**

1. SET and OT-TENS (OT with TENS) will produce significant improvements in pain and physical functioning in female FM patients.

2. SET and OT-TENS will produce significantly greater long-term improvements in pain assessed by numeric rating scale (NRS), pain severity, and physical functioning; in contrast to AE-BRT which, due to the lack of OT will have predominantly short-term benefits.

3. Improved BRS will be greater after SET and AE-BRT than after OT-TENS.

4. SET will produce significantly greater effects than the OT-TENS and AE-BRT groups on NRS pain, pain severity, BRS responses, and physical functioning.

## Patients and Methods

**Study participants**

The study was approved by the Ethics Committee of the Philipps-University Marburg, Germany. All psychological pain therapists had more than 15-years experience. The records of all participants were code-identified. Only the PI had access to identifying information.

A total of 128 female patients diagnosed with FM initially recruited from Internal Medicine and Rheumatology clinics in Germany were eligible enrollment in the trial (table 1). Inclusion criteria were elevated (1) pain behaviors, (2) pain-related interference, (3) solicitous spouse responses, (4) catastrophizing, and (5) low physical activity. Patients with a cardiac risk profile, with demonstrated hypertensive stress reactivity at baseline, and who did not manifest any significant psychiatric disorders, inflammatory diseases, intake of opioids, amitriptyline, current use of antihypertensive medications or centrally acting medication (i.e. gabapentin, pregabalin, duloxetine and milnacipran). Patients (29.4%) which took amitriptyline and/or selective beta-blockers, were asked to discontinue use 7 days before therapy begin.

**Study Protocol**

After informed consent, 62 patients were randomly assigned to the SET (N=21), OT-TENS, (N=20), or AE-BRT (n=21). Group assignment was randomized in blocks of 3 based on time of the year by a research assistant. This was a single-blind study, since it is not feasible to blind the therapist in the psychotherapeutic treatment; however, patients were blinded and outcome data were collected by a research assistant who was not aware of the treatment assignments (*Figure 2 - CONSORT diagram**[[32]](#endnote-32)).*

All patients (N=128) received medical and rheumatic assessments *(Table 1)*. The inclusion criteria were: (1) both the 1990 and 2011 ACR criteria[[33]](#endnote-33),[[34]](#endnote-34), (2) married or being in a relationship, and (3) willingness of the spouse to participate. The patients were randomized into treatment groups comparable with respect to age, education, body mass index, medication intake as an expression of pain behaviors, physical interference, solicitous spouse responses and physical activity. Significant differences in ‘number of painful regions’, ‘tender point intensity’ and BRS were found only between hypotensive FM patients and FM patients comorbid with personality disorders who were subsequently excluded from enrollment. Fifty patients completed the pre-, post- and follow-up (see *Figure 2*).

**Assessment**

**Physical assessment**

The physical assessment included blood chemistry analysis, neurological and Tender Point (TP) examination. The number of positive TPs and pain intensity of TPs were assessed using the Manual Tender Point Survey[[35]](#endnote-35).

**Psychometric Assessment**

Pain before T1, after T2, and 6-12 months after treatment T3 was assessed using a numeric rating scale, and the Multidimensional Pain Inventory[[36]](#endnote-36), self-report measure used previously in studies of FM[[37]](#endnote-37),[[38]](#endnote-38).

The MPI is a 60-item questionnaire assessing pain intensity, interference of pain, life control, affective distress, social support, significant-other responses, and general activity levels. The MPI has been widely used with diverse chronic pain patients (including FM) and has proven psychometric properties12,[[39]](#endnote-39),[[40]](#endnote-40).

All patients completed treatment expectation ratings before the first session and satisfaction ratings at the end of the first and last sessions[[41]](#endnote-41). Satisfaction was rated on a 6-point scale ranging from 0 ('completely unsatisfied') to 6 ('completely satisfied').

**Psychophysiological Recording of BRS**

BRS is calculated as a ratio of blood pressure (BP) and heart rate (HR) using the spectral method (<http://www.nevrokard.eu/maini/brs.html>). BP and HR was measured with a photoplethysmographic device (Finapress) on the middle finger of the left hand[[42]](#endnote-42).

**Treatment**

Each treatment consisted of two 2-hour sessions per week for 5 weeks, totaling 20 hours. Depending upon treatment protocol, the first hour in each session was spent on OT or AE, followed by an hour of BRT or TENS.

*Systolic Extinction Training - SET*

SET combines OT with BRT. OT, based on structured manuals33,[[43]](#endnote-43), was directed toward changing observable pain behaviors and included video feedback of expressions of pain, contingent positive reinforcement of pain-incompatible behaviors, and punishment of pain behaviors. Time-contingent exercises were provided[[44]](#endnote-44) in the sessions and as homework. The patients were accompanied by their spouse and engaged in role-playing to reduce pain behaviors and increase healthy behaviors. Patients were assigned homework that included instructions to increase activities and reduce pain behaviors. A reduction of medication dose was based on a physician-coordinated individual time-contingent interval plan. Spouses were invited to attend each 2nd session. The treatment was co-led by a psychologist and a rheumatologist.

In SET, after the OT, BRT was added. BRT consists of 2, 8-minutes-trials with both non-painful electrical stimuli and painful stimuli of 50% and 75% of the individual pain tolerance. BRT is administered to N. median on ring and index finger in randomized order *synchronized* with the cardiac cycle38.

*OT and cardiac-independent electrical stimulation – OT-TENS*

In OT-TENS, OT is combined with electrical stimulation that also consisted of 2, 8-minute trials in which the same electrical stimuli (non painful, 50% and 75% of the pain tolerance) were administered to N. median on ring and index finger. However, these stimuli were given *independently (e.g., non-contingent)* on cardiac cycle. OT-TENS was used as a control to assess the impact BRT had on pain reduction38.

*Aerobe exercises + BaroReflexTraining – AE-BRT*

AE consisted of moderate to vigorous intensity exercise on a cycle ergometer. Training sessions were 2 times per week for 5 weeks. AE sessions were 50 minutes in duration and consisted of 15-minute warm-up, 20-minute aerobic cycle ergometer training, and 15 minutes of cool down/stretching. The program used a target HR zone of 50% to 60% of maximal HR for the first 2 weeks, progressing to 80% to 85% of maximal HR for the remainder of the program. HRs were monitored at 60-second intervals throughout training using HR measurement attached to the ergometer. AE-BRT was included to determine the influence of OT on pain inhibition. The patients received the same introduction as the patients treated by SET and OT-TENS. AE-BRT was used to determine the influence of OT on pain inhibition.

*Treatment adherence*

Adherence to the treatments was assessed by the number of sessions attended. In addition, for SET and OT-TENS adherence was also assessed by completion of homework assignments. OT-TENS and AE-BRT patients were given the option of joining the SET group after their follow-up was complete.

*Therapists*

Two psychologists and a physiotherapist, with more than 15 years of experience, conducted the treatments. They completed a 2-day training program (provided by K.T.) together with 2 rheumatologists, 3 general practitioners, 3 psychologists in post-graduate training (supervised by K.T.) served as co-therapists. Additionally, psychologists, general practitioners, and rheumatologists met to decide discuss problems with motivation and non-adherence. The treatment sessions of SET and OT-TENS were video-recorded.

**Data analysis**

The adequacy of the sample size to test the primary outcome was calculated using G\*Power 3 to verify the interpretability and validity of the results. A total of 12 patients/group was determined to be adequate to test the primary hypothesis. Based on the calculation performed, the power was determined to be 0.857, the critical F value with df1= 2 and df2=9 is F = 4.256 with the following effect size Pain (MPI) f = 1.151.

**Statistical Analyses**

*Primary analyses*. The intent-to-treat principle guided the analyses such that the baseline scores for those who terminated treatment prematurely were carried forward [LOCF]. Sensitivity analyses were also conducted imputing baseline data for missing data (baseline observation carried forward [BOCF]). The co-*primary outcome* measures were changes in pain severity and physical pain-related interference[[45]](#endnote-45) 27at post-treatment and the 6-12-month follow-ups on the MPI pain and interference scales. The initial analyses of treatment effectiveness were assessed using a multivariate analysis of variance (MANOVA) for pain and function, and used a *P* value Bonferroni-adjusted to *P* < 0.013. Identification of significant main effects and interactions were followed by post hoc analysis of variance (ANOVA) with repeated measures and *t* tests.

Additionally, pain intensity was assessed before and after the experimental BRT protocol using single NRS ratings of pain intensity to identify the process of change in pain throughout the study. The ANOVA with repeated measures was performed with treatment groups as the between factor and 2 measure points (before and after the stimulation) assessed before (T1), after (T2) and 6-12 months after treatment (T3) as a within factor using a P value Bonferroni adjusted to *P* < 0.013. The differences of pain intensity before and after treatment for each group were calculated using *t*-Tests.

*Secondary analysis*. The psychophysiological variable BRS assessed as spectral BRS during BRT-protocol was calculated as secondary analysis to examine changes in BRS resulting from the treatments. The differences of the BRS in FM patients of SET, OT-TENS, and AE-BRT were calculated using ANOVAs with repeated measures of the stimulation in the BRT-protocol before (T1), after therapy (T2), and after 6-12 months follow-up (T3) by assessing significant main effects and time x group interactions after outlier rejection. For the outcome measures, a repeated measures ANOVA was performed with the treatment groups as the between factor and the stimulation as a within factor followed by Bonferroni-corrected t-tests using an adjusted *P* < 0.013. The baseline was used as a covariate since the groups were significantly different at baseline (see below).

*Additional Analyses*. The reliability change index[[46]](#endnote-46) was computed to calculate the percentage of responders for pain. The RC index is an empirical measure for the responder rate of the respective treatment. Finally, correlations between clinically significant pain reduction and BRS changes were calculated using Pearson correlation.

**Results**

**Attrition**

One patient in the SET (4.7%), 5 in the OT-TENS (25.0%), and 6 in the AE-BRT (29%) terminated prematurely (*Figure 2*). All dropouts occurred between sessions 1 and 4. The primary reason that patients gave for dropping out was deterioration of symptoms. Patients who terminated prematurely were not significantly different from those who completed treatment in demographic variables, duration of symptoms, or initial pain severity.

**Treatment expectation and adherence**

There were no statistically significant differences between thegroups in treatment expectations (F(2, 45) = 1.26, *P* = 0.29)assessed at the first treatment session. Analysis of treatment satisfaction was calculatedat the end of the last session; which revealed neither a significant group (F(2, 45) = 2.34, *P* =0.08) or a significant group × phase (first versus last session)(F(2, 45) = 0.82, *P* = 0.09) effect.

In the SET group, no sessions were missed and 98% of homework was completed. For the OT-TENS and AE-BRT groups 20% of sessions were missed. The subsample of the OT-TENS group who completed treatment completed 95% of the assigned homework.

**Primary outcomes**

Pain Severity and Interference (MPI).The MANOVA revealed a significant effect of the 3 groups (F(2,46) = 25.32, *P* < 0.001), outcome variables (F(2, 45) = 24.54, *P*< 0.001), time (F(2, 45) = 7.39, *P*= 0.002), and asignificant time × group (F(2, 45) = 8.38, *P* = 0.001) andtime xgroup × outcome variables (F(4, 44) = 5.38, *P* =0.002) interactions. There was no significant outcomevariable by time effect. The post hoc ANOVA revealed statistically significantdifferences between SET and OT-TENS (*P* < 0.001) and between SET and AE-BRT (*P* < 0.001), but not between OT-TENS andAE-BRT (*P* = 0.64).

Pain Severity

An ANOVA on MPI pain severity revealed a statistically significant group × time interaction (F(2, 46) = 20.07, *P* < 0.001) with significant differences between SET and both OT-TENS and AE-BRT (both *P*s < 0.001) with SET showing statistically significant reductions in pain (*Table 2*) immediately after and at the 6-12-month follow-up (both *P*s < 0.001). There were statistically significant differences between SET, OT-TENS, and AE-BRT, at the 6-month and 12-month follow-ups (all *P*s < 0.001) (Figure 3). OT-TENS showed a trend reduction of pain severity in T2 maintained in T3. Pain severity decreased significantly after AE-BRT (*P* = 0.043) but this reduction was not maintained at T3.

Pain-related Interference

The post hoc ANOVA on pain-related interference (MPI reference) revealed a statistically significant group × time interaction (F(2, 46) = 30.69, *P* < 0.001) (Table 2) with SET significantly different from OT-TENS and AE-BRT. Interestingly, only the groups that included OT showed a statistically significant decrease of functional limitations immediately after therapy (*P* < 0.01). Both SET and OT-TENS maintained the decreased interference at the 6-12-month follow-up, (*Figure 3*).

**NRS- Pain intensity**

The post-hoc ANOVA on NRS pain intensity revealed a statistically significant group × time interaction (F(2, 46) = 30.69, *P* < 0.001) (Table 2) with SET significantly different from both OT-TENS and AE-BRT (*P*<0.001). All SET treated patients reported being completely pain-free following treatment and 81% maintained this status at follow-up (*Figure 3*).

**BRS**

Consistent with the results for pain and functional impact, a repeated measures ANOVA yielded a significant group × time interaction (F(2, 46) = 9.78, *P* = 0.001) for BRS during 8-minutes-BRT protocol with statistically significant group differences between SET and OT-TENS (*P* = 0.029, *Figure 3*). However, the BRS level between SET and AE-BRT was not significantly different. The SET group showed a significant *increase* of BRS during BRT protocol with 57% immediately following treatment and 48% 6 - 12 months after treatment (both *P* < 0.01). Neither the AE-BRT nor the OT-TENS groups displayed any significant changes over time.

**Clinical Significance of the Improved and Deteriorated Variables.**

The RC index of the MPI pain severity scale showed a responder rate of 82.6% for the SET group compared to 39% for the OT-TENS group and 14% for the AE-BRT group (χ 2 [2] = 13.38, *P* = 0.001) 12-months following treatment. The percentage of SET and OT-TENS was significantly higher than that of the AE-BRT responders (*P* = 0.005). OT-TENS and AE-BRT responders differ significantly (*Figure 4*).

The RC index of the MPI interference scale revealed a responder rate of 96% for the SET group compared 60% for the OT-TENS group, and 28.6% for the AE+BRT group (χ 2 [2] = 20.26, *P* < 0.001) 12 months following treatment. The percentage of SET and OT-TENS was significantly higher than that of the AE-BRT responders (*P* < 0.001). OT-TENS and AE-BRT responders differ significantly from each other with OT-TENS having a greater and statistically significant percentage of responders (*P*< 0.01, *Figure 4*).

The RC index of the NRS pain scale showed a responder rate of 91% for the SET group, 46% for the OT-TENS group, and 53% for the AE-BRT group (χ 2 [2] = 11.19, *P* = 0.004) 12 months following treatment. The percentage of SET was significantly higher than that of the OT-TENS (*P* = 0.009) and the AE-BRT responders (*P* = 0.01). OT-TENS and AE-BRT responders did not differ significantly (*Figure 4*).

**Correlation between clinically significant pain reduction and BRS changes.**

The clinically significant changes in pain severity assessed by MPI-RC-index were negatively correlated with BRS changes immediately after treatment (r = - 0.51, *P* = 0.008). The BRS changes 6-12 months after therapy were negatively correlated with changes in pain intensity measured by NRS-RC-index (r = - 0.52, *P* = 0.008).

**Discussion**

This study evaluated the efficacy of SET combining OT with a cardiac-gated electrical stimulation (BRT). SET showed high efficacy for a subgroup of female FM patients with hypertensive profiles. SET displayed significantly greater reductions in pain intensity and pain-related interference than in patients who were treated with OT-TENS (i.e., cardiac independent peripheral electrical stimulation). OT is an effective treatment of FM, with modest reductions in pain severity. However, when OT is combined with BRT, 44% more patients reduced their pain by 50% for more 6-12 months following treatment. *SET* reached a pain remission in 100% of the patients immediately after treatment which held in 82% of the patients for more than 12 months.

Both treatment groups that targeted pain behaviors (i.e., OT) produced significantly greater long-term improvements in pain (NRS), pain severity, and physical functioning (both MPI) versus cardiovascular fitness training (AE) even when it was combined with BRT. The results of long-term improvements in pain and physical functioning with OT show the importance of including a behavioral component in chronic pain treatment[[47]](#endnote-47),[[48]](#endnote-48),[[49]](#endnote-49).

Also confirming our hypothesis, patients treated with BRT with either SET or AE increased their originally diminished BRS and had greater pain reduction immediately after treatment than patients who did not receive BRT (i.e., OT-TENS). In contrast to SET, the physical conditioning treatment (AE) did not maintain BRS at the follow-up. Furthermore, the pain reduction after AE-BRT was maintained at follow-up for only 14% in contrast to 82% of SET responders. Interestingly, AE responders showed significantly lower pain before the treatment compared to the non-responders (*P* < 0.01). This result replicates studies reporting that only patients with lower pain intensity (< 3, NRS 0-10) appear to profit from AE26. Future studies might determine whether the addition of BRT to cardiovascular training can improve the efficacy of physiotherapy in patients with lower pain intensity.

Our hypothesis regarding the long-term effects in BRS and pain inhibition after SET was also confirmed. The combination of (1) practicing healthy behaviors provokes cortical changes of pain inhibition with (2) BRS that provokes subcortical and brainstem changes, resulted in pain freedom for 82% of the patients at the 12-month follow-up. This clinically significant pain reduction was significantly correlated with BRS reactivation (r=0.52) and restored the inverse relationship of pain and BRS comparable to observed in healthy people21,16. BRS increased by 57% immediately after SET and maintained at 48% for more than 12 months. The resulting level of BRS, 10.2 ms/mmHg, was comparable to that observed in healthy individuals[[50]](#endnote-50), Future studies may investigate the influence of NTS reflex arcs on the cortical pain network. From the clinical perspective, SET can achieve complete pain relief in a targeted subgroup of female FM patients.

FM patients with avoidant personality disorder showed a higher number of painful regions, a higher tender point intensity, and a higher BRS than the FM patients without PD. Future studies with larger samples should investigate whether higher BRS, despite higher pain perception and hypertensive blood pressure reactivity in FM-PD patients, might have mechanisms and pathways that are similar to psychiatric diseases observed in chronic pain disorders.

Although the sample size in this study was relatively small, a power analysis confirmed the numbers were adequate to test our primary hypotheses.

**Conclusions**

SET resulted in clinically significant and long-lasting remission of pain and physical interference compared to OT-TENS and AE-BRT for female FM patients with significant deficiencies in baroreceptor sensitivity. Additional research with larger samples and other chronic pain conditions is warranted to confirm and extend these results.

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**Competing interests:** The authors declare that they have no competing interests.

References

Table1: Demographic and clinical data of the patients (N=128)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | SET  (N=21)  M  SD  (Range) | OT+TENS  (N=20)  M  SD  (Range) | AT+BRT  (N=21)  M  SD  (Range) | FM with BP↓  (N=50)  M  SD  (Range) | FM with PD  (N=16)  M  SD  (Range) | \*  \*\* |
| Age  (in years) | 51.57  9.06  (34 – 67) | 56.17  9.82  (40 – 79) | 52.06  10.49  (35 – 74) | 54.36  12.06  (28 – 68) | 55.67  12.00  (28-79) | ns.  ns. |
| Education N (%)  <10 years  13 years  University Degree | 13 (61.90)  4 (19.05)  4 (19.05) | 14 (70.00)  3 (15.00)  3 (15.00) | 14 (66.67)  6 (28.57)  1 (4.76) | 32 (64.00)  5 (10.00)  13 (26.00) | 10 (62.50)  3 (18.75)  3 (18.75) | ns.  ns. |
| Occupation N (%)  Working  Unemployed  Workers’ Compensation  Retired | 11 (52.4)  0 (0.0)  8 (38.1)  2 (9.5) | 9 (45.0)  0 (0.0)  9 (45.0)  2 (10.0) | 14 (66.7)  1 (4.8)  4 (19.0)  2 (9.5) | 42 (84.0)  4 (8.0)  2 (4.0)  2 (4.0) | 8 (50.0)  0 (0.0)  6 (37.5)  2 (12.5) | 0.0071  ns. |
| Duration of pain  (in years) | 14.67  14.32  (2 – 49) | 12.14  9.32  (1 – 28) | 16.00  7.04  (4 – 27) | 15.09  12.62  (2 – 41) | 15.08  11.78  (1 – 38) | ns.  ns. |
| Number of  painful regions | 8.55  6.24  (3 – 20) | 6.67  3.33  (3 – 12) | 4.45  2.51  (3 – 8) | 3.20  2.37  (3 – 6) | 10.50  8.21  (3 – 23) | 0.042  ns. |
| Number of  Tender Points | 15.00  2.77  (11 – 18) | 16.43  1.51  (12 – 18) | 15.36  1.85  (11 – 18) | 12.27  1.85  (11 – 14) | 16.33  1.61  (11 – 18) | ns.  ns. |
| Mean Tender Point Pain  Intensity | 5.46  2.57  (2 - 10) | 6.83  1.94  (3 - 8) | 5.36  1.34  (3 - 7) | 3.36  1.29  (1 - 5) | 7.77  1.42  (5 - 10) | 0.033  ns. |
| BMI | 27.13  4.31  (21.7–39.8) | 30.44  8.98  (19.1–49.8) | 31.67  6.16  (22.1- 42.6) | 26.38  3.59  (19.9–29.4) | 27.54  7.81  (20.2-48.7) | ns.  ns. |
| BRS | 6.60  2.89  (0.0 – 10.4) | 5.90  4.69  (1.69 – 11.9) | 6.86  3.37  (3.3 – 12.4) | 3.33  1.54  (1.6 – 4.4) | 9.72  5.27  (2.6 – 17.9) | 0.024  ns. |
| Entire Med  (n/day) | 3.36  2.24  (0 – 8) | 3.71  1.79  (1 – 6) | 2.93  1.39  (1 – 5) | 1.80  1.42  (0 – 4) | 2.92  2,15  (0 – 7) | ns.  ns. |
| Pain Meds  (n/day) | 1.27  0.79  (0 – 2) | 1.00  0.82  (0 – 2) | 1.07  0.79  (0 – 2) | 0.36  0.18  (0 – 1) | 0.92  0.79  (0 – 3) | ns.  ns. |
| Amitriptyline  (n/day) | 0.20  0.41  (0 – 1) | 0.57  0.54  (0 – 1) | 0.40  0.51  (0 – 1) | 0.36  0.67  (0 – 2) | 0.25  0.45  (0 – 1) | ns.  ns. |
| Beta-Blocker  (n/day) | 0.27  0.47  (0 – 1) | 0.29  0.49  (0 – 1) | 0.13  0.35  (0 – 1) | 0.00  0.00  (0 – 0) | 0.17  0.39  (0 – 1) | ns.  ns. |
| Interference (MPI) | 3.24  1.38  (0.9 – 5.4) | 4.46  0.69  (3.7 – 5.3) | 3.55  1.20  (0.4 – 5.3) | 4.01  1.11  (1.8 – 5.4) | 4.24  0.83  (2.9 – 6.0) | ns.  ns. |
| Solicitous spouse response (MPI) | 3.53  1.55  (1.6 – 6.0) | 2.94  1.54  (0.2 – 4.4) | 3.19  1.24  (0.8 – 5.6) | 2.68  1.39  (0.2 – 2.4) | 2.63  1.83  (0.2 – 2.8) | ns.  ns. |
| Physical activity (MPI) | 3.03  0.78  (1.5 – 4.3) | 2.66  0.53  (1.8 – 3.2) | 2.42  0.71  (1.1 – 3.5) | 2.56  0.48  (1.8 – 3.2) | 2.38  0.72  (0.9 – 3.2) | ns.  ns. |

AT+BRT - Aerobic Training and BaroreflexTraining, BRS - Baroreflex Sensitivity, FM with BP↓ - Fibromyalgia without any hypertension or with hypertensive blood pressure stress response, OT+TENS - operant therapy and transcutaneous electrical nerve stimulation, FM with PD - Fibromyalgia with Personality Disorders, SET - Systolic Extinction Training; \* - Significant Differences between all groups, \*\* - Significant differences between the treatment groups

1Significantly more hypotensive FM patients worked compared to SET (*P* = 0.016), OT\_TENS (*P* = 0.004) and FM\_PD (*P* = 0.024) groups that were not unemployed (SET and OT\_TENS: *P’s* = 0.044) but have received more frequent worker’s compensation (SET: *P* = 0.015, OT\_TENS: *P* =0.005, FM\_PD: *P* = 0.037).

2FM\_PD patients reported a higher number of painful regions in comparison to hypotensive FM patients (*P* = 0.036).

3FM\_PD patients displayed a higher tender point intensity compared to hypotensive FM patients (*P* = 0.027).

4FM\_PD patients showed a higher BRS in comparison to hypotensive FM patients (*P* = 0.024).

**Table 2**. Means, SDs, and F and *P* values for ANOVA effects for group, time, and group × time (G × T) and T and *P* values for the main outcome variables

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome variables ANOVA - Main effects T - tests | | | | | | | | | | | | | | | |
| Outcome variables | Group | Pre-  treatment  Mean (SD)  [CI] | Post-treatment  Mean (SD)  [CI] | 6 - 12-month f/u  Mean (SD)  [CI] | | Group  F  *P* | | Time  F  *P* | | G × T  F  *P* | | T1 vs. T2  T  *P* | | T1 vs. T3  T  *P* | | |
| **MPI-Pain** | SET | 3.39 (1.29)  [2.92|3.85] | 0.77 (0.61)  [0.41|1.13] | 0.58 (0.76)  [0.15|1.01] | |  | |  | |  | | 8.23  <0.001 | | 8.01  < 0.001 | | |
|  | OT\_TENS | 4.40 (0.58)  [3.76|5.04] | 3.77 (0.77)  [3.27|4.26] | 3.90 (0.67)  [3.31|4.48] | |  | |  | |  | | 1.93  0.08 | | 1.87  0.09 | | |
|  | AT\_BRT | 3.51 (0.76)  [2.99|4.03] | 2.93 (0.94)  [2.53|3.34] | 3.20 (1.20)  [2.72|3.68] | | 68.02  >0.001 | | 23.81  <0.001 | | 20.07  <0.001 | | 2.23  0.04 | | 1.02  ns. | | |
| SET vs. OT+TENS | | Bonferroni – Correction  < 0.001 | | | | | | | | | |  | |  | | |
| SET vs. AT+BRT | | < 0.001 | | | | | | | | | |  | |  | | |
| OT+TENS vs. AT+BRT | | <0.010 | | | | | | | | | |  | |  | | |
| **MPI- Physical Functioning** | SET | 3.24 (1.39)  [2.69|3.78] | 0.80 (0.73)  [0.34|1.26] | 0.60 (0.56)  [0.14|1.06] | |  | |  | |  | | 8.59  <0.001 | | 8.80  < 0.001 | | |
| OT+TENS | 4.58 (0.51)  [3.83|5.34] | 3.86 (1.08)  [3.22|4.49] | 4.07 (0.88)  [3.44|4.69] | |  | |  | |  | | 2.25  0.04 | | 2.33  0.04 | | |
|  | AT+BRT | 3.55 (1.20)  [2.94|4.17] | 2.89 (1.22)  [2.37|3.41] | 2.98 (1.40)  [2.47|3.50] | | 30.69  >0.001 | | 26.89  <0.001 | | 18.11  <0.001 | | 2.59  0.02 | | 1.92  ns. | | |
| SET vs. OT+TENS | | Bonferroni – Correction  < 0.001 | | | | | | | | | |  | |  | | |
| SET vs. AT+BRT | | < 0.001 | | | | | | | | | |  | |  | | |
| OT+TENS vs. AT+BRT | | ns. | | | | | | | | | |  | |  | | |
| **NRS-Pain** | SET | 32.81 (18.07)  [23.13|42.50] | 3.75 (5.92)  [-3.99|11.49] | 2.56 (5.45)  [-5.61|10.73] | |  | |  | |  | | 6.59  <0.001 | | 6.53  <0.001 | | |
|  | OT+TENS | 43.85 (20.93)  [33.09|54.59] | 31.92 (23.05)  [23.33|40.52] | | 28.85 (22.38)  [19.78|37.91] | |  | |  | |  | | 1.32  ns. | | 2.11  <0.05 | | |
|  | AT+BRT | 33.00 (18.78)  [22.99|43.01] | 29.27 (14.02)  [21.27|37.27] | 26.67 (17.49)  [18.23|35.11] | | 11.73  >0.001 | | 14.74  >0.001 | | 5.35  0.009 | | 0.79  ns. | | 1.68  ns. | | |
| SET vs. OT+TENS | | Bonferroni-Correction  < 0.001 | | | | | | | | | | | | | | |
| SET vs. AT+BRT | | 0.003 | | | | | | | | | | | | | | |
| OT+TENS vs. AT+BRT | | ns. | | | | | | | | | | | | | | |
| **BRS** | SET | 6.86 (2.68)  [5.44|8.28] | 10.76 (3.87)  [8.72|12.79] | 10.18 (4.98)  [7.85|12.49] | |  | |  | |  | | -5.23  <0.001 | | -3.09  0.009 | | |
|  | OT+TENS | 5.72 (1.96)  [4.02|7.42] | 5.67 (2.05)  [3.21|8.12] | 5.52 (1.90)  [2.73|8.31] | |  | |  | |  | | 0.19  ns. | | 1.08  ns. | | |
|  | AT\_BRT | 6.34 (2.65)  [4.87|7.81] | 7.16 (4.14)  [5.04|9.28] | 7.51 (4.21)  [5.10|9.93] | | 8.01  0.027 | | 8.01  0.002 | | 9.78  0.001 | | -1.03  ns. | | -1.30  ns. | | |
| SET vs. OT+TENS | | Bonferroni – Correction  0.029 | | | | | | | | | |  | |  | | |
| SET vs. AT+BRT | | ns. | | | | | | | | | |  | |  | | |
| OT+TENS vs. AT+BRT | | ns. | | | | | | | | | |  | |  | | |

Comparisons refer to pre-treatment, post-treatment, and 6 - 12-month follow-ups in the SET, OT+TENS, and AT+BRT groups. ANOVA - analysis of variance; AT+BRT - aerobe training + BaroReflexTraining; BRS - Baroreflex Sensitivity; CI - Confidence Interval; f/u - follow-up; MPI - Multidimensional Pain Inventory; NRS pain - pain on numeric rating scale (0 – 100); ns. - not significant; OT+TENS - operant behavior therapy + transcutaneous electrical nerve stimulation; SET - systolic extinction training; SD - standard deviation.

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