
Prolonged treatment with transcutaneous electrical nerve stimulation (TENS) modulates neuro-gastric motility and plasma levels of vasoactive intestinal peptide (VIP), motilin and interleukin-6 (IL-6) in systemic sclerosis

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ABSTRACT

Purpose. We assessed the effects of transcutaneous electrical nerve stimulation (TENS) on neurogastric functioning in scleroderma patients.

Methods. Seventeen SSc patients underwent 30 min TENS treatment >10Hz at GI acupuncture points PC6 and ST36, once (acute TENS) and then after two weeks of TENS sessions for 30 min twice daily (prolonged TENS). Data collected at Visits 1 and 2 included gastric myoelectrical activity (GMA) by surface electrogastrography (EGG), heart rate variability (HRV) by surface electrocardiography (EKG), GI specific symptoms and health-related SF-36 questionnaires. Plasma VIP, motilin and IL-6 levels were determined. Statistical analyses were performed by Student's *t*-test, Spearman Rank and *p*-values <0.05 were considered significant.

Results. 1. Only after prolonged TENS, the percentages of normal slow waves and average slow wave coupling (especially channels 1, 2 reflecting gastric pacemaker and corpus regions) were significantly increased; 2. the percentage of normal slow waves was significantly correlated to sympathovagal balance; 3. Mean plasma VIP and motilin levels were significantly decreased after acute TENS, (vs. baseline), generally maintained in the prolonged TENS intervals. Compared to baseline, mean plasma IL-6 levels were significantly increased after acute TENS, but significantly decreased after prolonged TENS. 4. After prolonged TENS, the frequency of awakening due to abdominal pain and abdominal bloating were significantly and modestly decreased, respectively.

Conclusion. In SSc patients, two weeks of daily TENS improved patient GMA scores, lowered plasma VIP, motilin

and IL-6 levels and improved association between GMA and sympathovagal balance. This supports the therapeutic potential of prolonged TENS to enhance gastric myoelectrical functioning in SSc.

Introduction

Ninety percent of patients with systemic sclerosis (SSc, scleroderma) complain of at least one gastrointestinal (GI) symptom of gastric and/or intestinal hypomotility (1-5). Gastric hypomotility is reflected in upper GI symptoms (6-10) and by abnormalities in the gastric myoelectrical activity (GMA), including significant alterations in the percentages of normal gastric slow waves and slow wave coupling, as detected by electrogastrography (EGG) (9, 10). The neurogenic contribution to SSc organ pathogenesis has been previously reported (11). Increased plasma norepinephrine, vasoactive intestinal peptide (VIP) and motilin levels have been reported in SSc (12-14).

Transcutaneous electrical nerve stimulation (TENS) is well established as a pain relieving modality for musculoskeletal complaints (reviewed in 15, 16). Non-nociceptive fibres are reported to be selectively stimulated, which inhibit the release of pain inducing neurotransmitters from nociceptive fibres (15-17). Pharmacologic and physiologic studies provide evidence that TENS induced anti-hyperalgesia is mediated centrally by activation of opioid, serotonergic and cholinergic receptors. This is achieved via central release of opioid peptides such as β -endorphin with analgesic and vasodilatory properties (18). Stimulation of afferent fibres in deep tissue is thought to be important in mediator release for central pain processing (18, 19). Elec-

trostimulation of the brain at different frequencies has also been reported to modulate additional neuropeptides of the opioid and orphanin systems and substance P (20).

Acupuncture is also believed to generate its therapeutic effects by the release of neuropeptides including endogenous opioids. In animal models, pretreatment with naloxone, a mu opioid antagonist with anti-adrenergic properties blocked the salutatory effects of acupuncture on colitis-induced diarrhea and vasopressin-induced emesis (16, 21, 22).

In a previous study of SSc patients, we reported sustained changes in the GMA after 30 minutes of acupressure applied to the GI acupuncture point (acupoint) PC6, changes not seen at control acupuncture point, PC10 (10). We have since reported improved sympathovagal ratios and perceived physical functioning after daily application of TENS to GI acupoints for two weeks (prolonged TENS, 23). We hypothesised that prolonged TENS treatment would consequently also modulate GMA and plasma GI peptides in these patients. To this end, we analysed the effect of acute compared to prolonged TENS application to GI acupoints on GMA, patient responses to a GI-related symptoms questionnaire and plasma levels of VIP, motilin and IL-6. We also analysed GMA and sympathovagal balance which was derived from the assessment of heart rate variability (HRV) within Visit 1 and Visit 2 to assess dynamic changes in neuro-gastrointestinal interactions between acute and prolonged TENS treatments. This study provides further evidence that neurally-mediated modalities are of potential therapeutic benefit to GI dysmotility in SSc patients.

Methods

Patient enrolment

The study was an open-label design; all patients received the same therapy and acted as their own controls. The research protocol was approved by the University Institutional Review Board and written informed consent was obtained from all subjects before study entry. Seventeen SSc patients who met the American College of Rheumatol-

ogy Preliminary Criteria for Scleroderma (24) were enrolled in the study (14 females and 3 males). As most patients with SSc report at least one GI symptom, patients were not screened for GI symptoms prior to study entry. All patients abstained from prokinetic agents for 72 hours and fasted for ≥ 6 hours before the initiation of the study. Patients were excluded if they: 1) were unable to give informed consent; 2) were currently taking prokinetic, anticholinergic or dopaminergic agents which could potentially modify gastric motility; 3) were unable to recline with a head elevation of 30 degrees; 4) had a history of abdominal surgery that could distort cutaneous landmarks for EGG lead placement; 5) were pregnant or preparing to conceive a child during the study period. One patient was mildly glucose intolerant and treated by diet alone. Otherwise, no patient had a history of diabetes mellitus.

Acute and prolonged TENS

Two-channel TENS electrodes were applied bilaterally to PC6 and ST36 GI acupoints. Three consecutive 30 minute intervals were measured in two study visits. The first visit, V1, is referred in this study as "acute TENS", to reflect patients at study entry who were initiated with a single TENS treatment, but otherwise naïve to TENS. The second study visit, V2, was performed two weeks later and is referred to as "prolonged TENS", to reflect the precedent two weeks of home TENS treatment performed by the patient. At the study visits, first, patients were asked to fill in the questionnaires, followed by continuous recording of GMA and HRV during five intervals of 30 minutes each. During the baseline (BsL) interval, recordings were performed with the TENS unit turned off and also served as the "sham" recording (see below). This was followed by the (TENS) interval, where actual TENS was applied and recovery (REC) interval, where the TENS electrodes stayed in place, but the unit was turned off. The patients were allowed to rise to a sitting position for 15 minutes to ingest a standardised 500 kcal test meal (20% fat, 30% protein and 40% carbohydrate)

with 100 ml of a non-caffeinated, non-carbonated beverage (9). The test meal was immediately followed by the last postprandial (POST) interval, in the same preprandial reclining position with the TENS unit turned off. The Second Visit (V2) measured the GMA, HRV and the questionnaire scores in the same manner as the V1 visit.

The electrical stimulus of the TENS unit consisted of pulse trains. The frequency and duration of the train was 12/min and 2 sec, respectively and pulses in each train had a frequency of 25 Hz all constant for the duration of the study. The stimulus had an amplitude range of 2–10 mA, and was based on patient tolerance. At the end of V1, patients were trained in the operation of the unit and lead placement of the TENS electrodes for home use (detailed in appendix). On days 2–14, the patients performed TENS at home twice a day for 30 minutes each, preprandially, before breakfast and the evening meal. Patients filled out a daily log to report their TENS use and were contacted by phone after the first seven days to confirm their use and correct placement of TENS leads.

Multi-channel surface electrogastrography (EGG)

Non-invasive assessment of gastric slow waves by EGG has been established and validated. The rhythmicity of gastric slow waves is accurately measured in the electrogastrogram and represented in the spectral analysis of the EGG (Reviewed in 25, 26). Surface EGG was recorded using a multi-channel recording device (Medtronic, Shoreview, MN), which is an FDA-approved clinical instrument. The device consists of four identical amplifiers (channels 1–4) with cut-off frequencies of 1.8 and 16.0 cycles per minute (cpm) that measure gastric slow wave propagation (27, 28). The GMA is composed of the rhythmic slow wave (also called electrical control activity, reflecting pacemaker potential) and spikes (electrical response activity or action potentials).

Heart rate variability (HRV)

To measure HRV, an electrocardiogram (EKG) was recorded concomitantly

with EGG. The recorded EKG signal was then amplified with a cutoff frequency of 50 Hz (model 2283 FTI universal Fetrotde amplifier; UFI, Morro Bay, CA). The signal was then sampled to 6000Hz, then 500Hz. HRV signal was derived from the EKG signal using our laboratory HRV analyser program (23).

We then ran the spectral analysis of the HRV signal and calculated the following parameters, as previously described (23): 1) the percentage of power in the low-frequency (LF) band (0.04 to 0.15 Hz) representing mainly the sympathetic activity, 2) the percentage of power in the high-frequency (HF) band (0.15 to 0.50 Hz) representing solely the vagal activity, and 3) the ratio of LF/HF representing the sympathovagal balance.

GI-dysmotility questionnaire

The GI Dysmotility Questionnaire (GIDQ) was developed by us to assess GI related symptoms and quality of life as the recently published GI-focused questionnaires for SSc patients (GIT 1.0), or GIT 2.0 were not validated or available at the time of this study (29, 30). We designed our 48 item questionnaire to assess upper and lower GI symptoms based on previous literature (31, 32). This questionnaire is described in detail elsewhere (14, 23) and includes "yes" and "no" and VAS-type, scored 0–100 mm, responses from the patients. It assesses prevalence, frequency and intensity of GI related symptoms. The GIDQ has not been validated in any patient population.

Self-perceived physical and mental functioning

The Medical Outcome Study Short Form-36 (SF-36, with 4 week recall), Version 1.0 was used to evaluate patient health related quality of life. The SF 36 is a well standardised 36 item survey instrument designed to evaluate QOL issues by self-perceived psychological and physical limitations due to an underlying illness and previously validated in SSc (33–35). Raw SF-36 version 1.0 domain scores were normalised to the current version (2.0) using a 2.0 conversion kit (SF Health Outcomes

Scoring Software, Quality Metric Incorporated, Lincoln, RI). The converted data obtained can be compared with normative data for the U.S. population as well as 2.0 version scores from other studies of rheumatic diseases.

Skin scores and Medsger Severity Index

The extent of skin involvement was assessed by the modified Rodnan skin score (mRSS, also called total skin score) as the sum of the scores of 17 body areas ranging from 0–3 per area and a total range 0–51, (36).

Medsger severity index scores (MSS) were assessed (37, 38). The severity scores were totaled from 9 subscales including: General, Peripheral Vascular, Skin, Joint/Tendon, Muscle, GI Tract, Lung, Heart and Kidney. Clinical damage was scored on a scale of 0–3 to cover parameters representing no involvement, or normal, to severe or end stage involvement.

Fasting plasma level determinations: vasoactive intestinal peptide (VIP), motilin and interleukin 6 (IL-6)

Fasting plasma samples were collected in EDTA containing tubes from the study subjects. Aliquoted samples were stored at –80 degrees Celsius and thawed only once for determination of vasoactive intestinal peptide (VIP), motilin and interleukin 6 (IL-6). Blood was drawn just before initiation of EGG testing at the baseline interval during the first study visit (V1) and just after the recovery interval, 30 minutes after TENS treatment during the first (V1, acute TENS) and second (V2, prolonged TENS) study visits. ELISA based assays were performed on plasma samples in duplicate according to manufacturers protocol for a sensitivity detection range of 0–25 ng/ml and 0–25 pg/ml for VIP and motilin, respectively, (Bachem, San Carlos, CA). IL-6 immunoassays were performed on plasma samples in duplicate according to manufacturer's protocol for a sensitivity detection range of 0–25 pg/ml (R&D Diagnostics, Minneapolis, MN). Human VIP ELISA and human motilin ELISA assays were performed on plasma samples in duplicate according

to manufacturers' protocol for a sensitivity detection range of 0–25 ng/ml and 0–100 pg/ml for VIP and motilin, respectively, (Bachem, Torrance, CA). IL-6 immunoassays were performed on plasma samples in duplicate according to manufacturer's protocol for a sensitivity detection range of 0–100pg/ml (R&D Diagnostics, Minneapolis, MN).

Statistical analysis

The percentages of normal slow waves, percentages of bradygastria, percentages of tachygastria, percentages of arrhythmia and percentages of slow wave coupling were assessed in this study. Multi-channel EGG results, questionnaire scores and plasma peptide levels are reported as mean values $\pm$ standard error and analysed by Student's *t*-test. Correlational analyses were performed by Spearman Rank Order (Statistica, software, Tulsa, OK). The analyses were performed on GMA derived from EGG recordings and sympathovagal balance, derived from HRV performed on clinical visits 1 and 2, which were separated by 2 weeks. The values were then plotted based on clinical visit, to assess correlational relationships within that visit. Values to correlational values of poor to excellent were derived according to Fleiss *et al.* (39). A value of $p < 0.05$ was considered significant.

Results

Patient demographics

The average age of enrolled patients was 55 ± 2.28 years. Females enrolled ($n=14$), comprised 82% of the SSc patients. The SSc patients diagnosed with diffuse cutaneous involvement ($n=9$) comprised 53% of the SSc patients. The average duration of systemic sclerosis at study entry was 8.88 ± 1.1 years (range: 2–18 years). The average mRSS for the SSc patients was 10.18 ± 1.3 (range: 3–21 and average Medsger Severity Score (MSS) Index was 7.76 ± 0.8 (range: 2–14).

Prolonged TENS increased percentage of gastric slow waves and percentage of slow wave coupling

Figure 1 demonstrates average percentages of GMA variables for baseline and postprandial intervals in V2 (prolonged

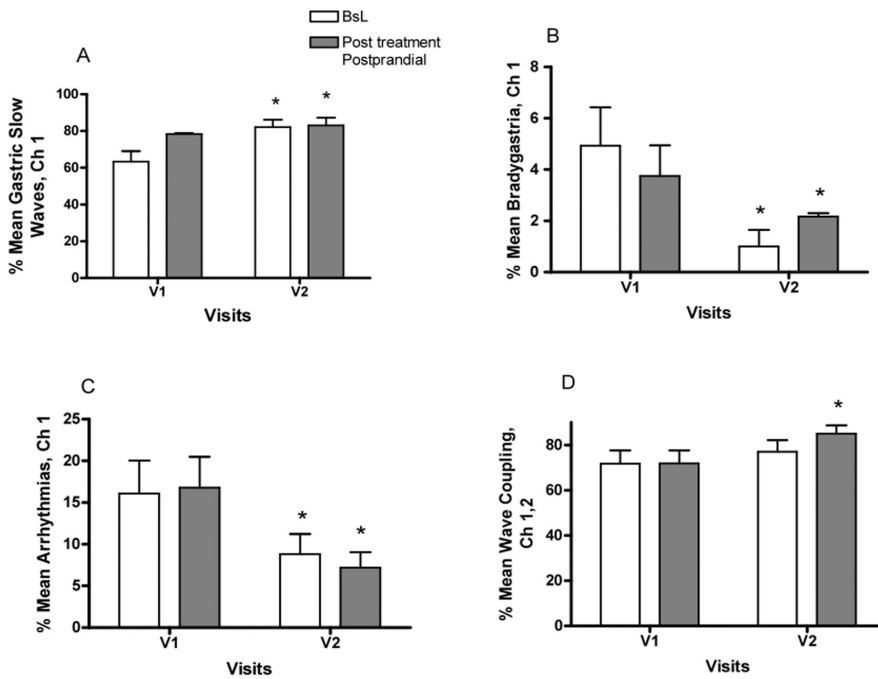


Fig. 1. The percentage of mean gastric waves obtained by surface EGG during baseline (BsL), TENS, recovery (Rec) and postprandial (POST) intervals of acute (V1) and prolonged (V2) TENS treatments in SSc patients. The recordings were derived from Channel 1 (Ch 1), reflecting the gastric corpus. **1A.** The percentage of mean slow waves. **1B.** The percentage of mean arrhythmias. **1C.** The percentage of mean bradygastria. **1D.** The average gastric slow wave coupling between channels 1 and 2 (Ch 1,2). * $p < 0.05$, V2 compared to V1.

TENS) compared to V1 (acute TENS) from channel 1, reflecting the region that contains the gastric pacemaker. Significant increases in the percentages of normal slow waves were noted in V2 compared to V1 for baseline (BsL, $82.1 \pm 4.2\%$ vs. $63.4 \pm 5.6\%$, respectively, $p = 0.02$) and modest increases in postprandial intervals ($83.05 \pm 4.29\%$ vs. $78.4 \pm 0.49\%$, respectively, $p = \text{NS}$), shown in Fig 1A. Additionally, modest increases in percentages of slow waves were noted in V1, during the acute TENS, recovery and postprandial intervals (71.3 ± 0.89 , 73.7 ± 0.54 , 78.4 ± 0.49 , respectively, $p = \text{NS}$, not shown). Significant decreases in the percentages of bradygastria were also noted in V2 compared to V1 in baseline and postprandial intervals as shown in Fig. 1B, (1.0 ± 0.85 vs. 4.93 ± 1 , respectively, $p < 0.02$ and 2.17 ± 0.13 vs. 3.75 ± 1.2 , respectively, $p < 0.05$). Concomitantly, significant decreases in the percentages of arrhythmia were noted in V2 compared to V1 in baseline and postprandial intervals shown in Figure 1C, (8.82 ± 2.4 vs. 16.07 ± 3.96 , respectively, $p = 0.01$ and 7.19 ± 1.8 vs. 16.78 ± 3.7 ,

respectively, $p = 0.02$). Significant increases were also observed in the percentage of slow wave coupling between channels 1 and 2 during the postprandial interval in V2 compared to V1 as demonstrated in Fig. 1D (85.0 ± 3.7 vs. 71.3 ± 5.7 , respectively, $p = 0.02$). A similar pattern of significant increases was observed in mean percentages of slow wave coupling between channels 2 and 3, channels 3 and 4 and channels 1 and 4 during V2, compared to V1 (not shown). There were modest increases in the percentage of slow wave coupling in V1 TENS, recovery and postprandial intervals (77.98 ± 4.75 , 75 ± 5.12 and 71.9 ± 5.7 , respectively, $p = \text{NS}$). Historical intra-patient values between V1 and V2 served as controls and showed the baseline V1 and V2 values to be very close at study visits for percentage of slow waves (97.5%) and percentage of wave coupling (93%, 10).

Both acute and prolonged TENS modulated plasma levels of VIP, motilin and IL-6

Figure 2 demonstrates the levels of plasma VIP, motilin and IL-6 after acute

and prolonged TENS treatments. In Fig. 2A, the average plasma VIP levels were significantly decreased after V1 recovery interval (18.5 ± 0.7 ng/ml, after the acute TENS interval) compared to the V1 baseline interval (23.5 ± 0.5 ng/ml, $p < 0.01$). The average plasma VIP levels after the recovery interval at V2 (after prolonged TENS) were also depressed (20.5 ± 0.6 ng/ml), compared to the V1 baseline interval, as shown.

Fig. 2B demonstrates the levels of plasma motilin after acute and prolonged TENS treatments. The average plasma motilin levels were significantly decreased after V1 recovery interval (10.54 ± 1.23 pg/ml, after the acute TENS interval) compared to the V1 baseline interval (18.2 ± 4.26 pg/ml, $p < 0.01$). The mean plasma motilin level the V2 recovery interval was 14.0 ± 2.06 pg/ml.

Figure 2C demonstrates the fluctuations in the levels of plasma IL-6 after acute and prolonged TENS treatments compared to the V1 baseline interval. In contrast to plasma VIP and motilin

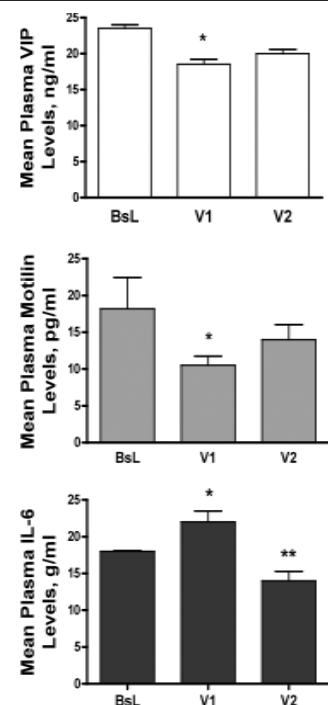


Fig. 2. Plasma levels of VIP, motilin and IL-6 obtained at baseline and after acute and prolonged TENS treatment in SSc patients. **2A.** Mean VIP levels, in ng/ml, **2B.** Mean plasma motilin levels, in pg/ml; **2C.** mean IL-6 levels in pg/ml. * $p < 0.05$ compared to baseline (BsL). ** $p < 0.05$ V2 compared to V1 BsL.

levels, the average levels of plasma IL-6 increased significantly in V1 after acute TENS treatment (22.5 ± 1.5 pg/ml), compared to “sham” treatment during the baseline interval (18.2 ± 1.3 pg/ml, $p < 0.04$). In V2 after prolonged TENS treatment, the mean IL-6 levels were significantly decreased compared to the V1 baseline (14.3 ± 1.0 pg/ml, $p < 0.05$) and V1 recovery ($p = 0.03$). Spearman Rank Order analyses determined that plasma IL-6 levels significantly inversely correlated with the percentages of normal slow waves ($R = -0.53$, $p < 0.03$) and slow wave coupling ($R = -0.54$, $p = 0.02$).

Prolonged TENS improved GI symptoms

Fig. 3A demonstrates improvements noted in reported GI related symptoms by the GIDQ in V2 compared to V1 to the question “Have you awakened in the middle of the night because of abdominal pain in the past seven days?” (0.54 ± 1.4 vs. 0.90 ± 0.07 , respectively, $p = 0.04$). Modest improvements (non-significant) in GIDQ scores between V2 and V1 were also noted with the following questions: “Do you experience a sensation of gas and/or bloating in the abdomen?” (0.20 ± 0.09 vs. 0.64 ± 0.11 , respectively, $p = 0.08$), and “Have you increased a clothes size or adjusted your clothes for abdominal bloating?” (0.29 ± 0.11 vs. 0.53 ± 0.12 , respectively, $p = 0.09$) and “Have you had to change any normal daily errand or task you usually perform at home or work because of GI symptoms?” (0.29 ± 0.12 vs. 0.53 ± 0.11 , respectively, $p = 0.09$).

The range in scores was 0-5 days for the frequency of abdominal pain/week reported in our SSc patients. Overall, in the patients who reported abdominal pain at V1, the frequency of reported abdominal pain decreased by 11 days among 5 patients, increased in 2 patients and was unchanged in 4 patients between V2 and V1. The patients with the most improved scores (0 days/week) on V2, reported abdominal pain on ≤ 3 days/week on V1 ($n = 3$).

Fig. 3B demonstrates the modest improvements in scores of Body Pain and Vitality domains in the SF-36 instrument in V2 compared to

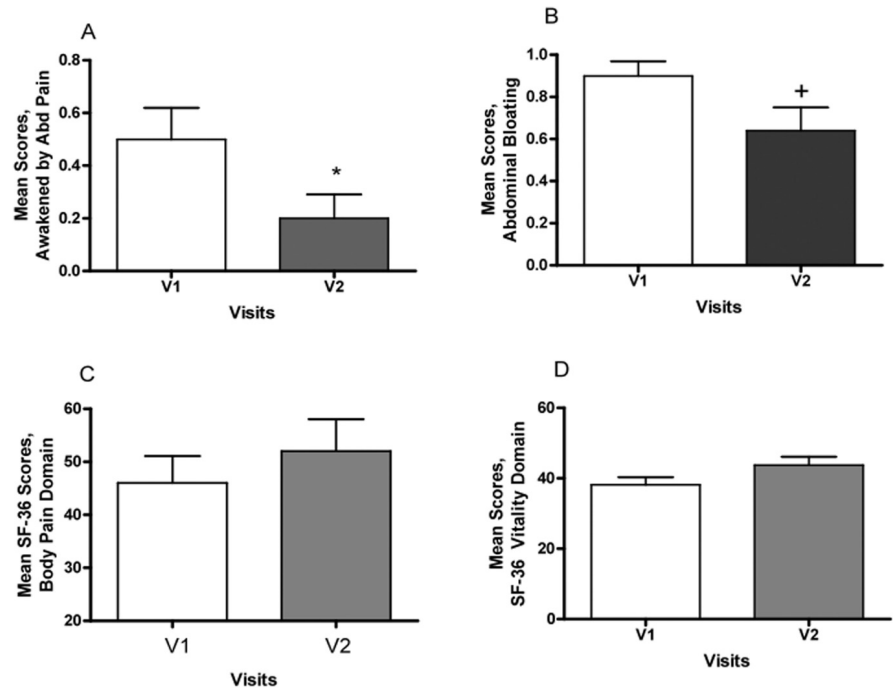


Fig. 3. Scores from GIDQ and SF-36 at V1 and V2 from SSc patients.

3A. GIDQ: GI Dysmotility Questionnaire: “Do you have abdominal bloating?” (yes/no) “Have you been awakened by abdominal pain in the past week?” (yes/no). Lower scores reflect improved GI related symptoms after prolonged TENS at V2; *: $p = 0.05$, compared to V1. +: $p = 0.08$, compared to V1. **3B.** The average SF-36 Bodily Pain domain scores at V1 and V2. Higher scores reflect improved Bodily Pain domain scores after prolonged TENS at V2.

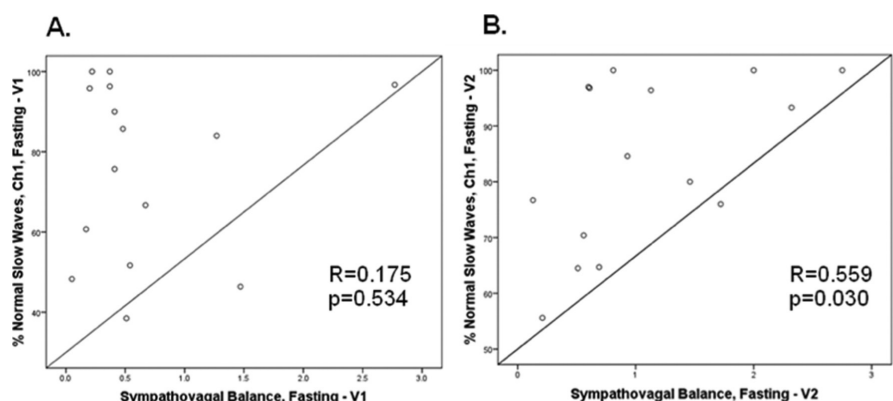


Fig. 4. Correlations between sympathovagal balance and percentage of normal slow waves channel 1 were performed by Spearman Rank Order. Recordings were from HRV and GMA determinations during EGG at baseline (fasting). **4A:** Visit 1 and **4B:** visit 2 demonstrate the development of significant association between sympathovagal balance and GMA after prolonged TENS treatment compared to acute TENS treatment from visit 1.

V1, (38.31 ± 2.50 vs. 40.2 ± 2.58 and 38.17 ± 2.25 vs. 43.07 ± 2.41 , respectively, $p = \text{NS}$). The SF-36 domain and summary scores between V1 and V2 were within 87% of each other.

Prolonged TENS improved GMA and sympathovagal coordination

Spearman Rank Order analyses were performed for correlational comparisons between sympathovagal balance

(measured by HRV, 23) and percentage of normal slow waves, channel 1 (measured by EGG) from visits 1 and 2. In fasting patients, significant correlations were seen between GMA and HRV parameters in V2, after prolonged TENS treatment. Figure 4A demonstrates the lack of correlation between the percentage of slow waves and the sympathovagal balance in V1 ($R = 0.175$, $p = 0.534$). However, in V2,

after prolonged TENS, a significant correlation was demonstrated between the percentage of normal slow waves and sympathovagal balance ($R=0.559$, $p=0.03$, Fig. 4B). Additionally, after prolonged TENS, the frequency of abdominal pain (by GIDQ) was significantly inversely correlated to the percentage of slow wave coupling ($R=-0.49$, $p=0.047$, compared to the lack of correlation in V1 ($R=0.25$, $p=0.34$).

Discussion

This study provides evidence that TENS electrostimulation to GI acupoints has physiologic and functional therapeutic potential in SSc GI dysmotility. We found that: 1. Only after prolonged TENS, the percentages of normal slow waves and slow wave coupling (especially channels 1, 2 reflecting gastric pacemaker and corpus regions) were significantly increased. 2. Mean plasma VIP and motilin levels were significantly decreased after acute TENS, (vs. baseline) and generally maintained in the prolonged TENS intervals. Compared to baseline, mean plasma IL-6 levels were significantly increased after acute TENS, but significantly decreased after prolonged TENS. 3. After prolonged TENS, the frequency of awakening due to abdominal pain significantly decreased. Improvements in abdominal bloating scores were also noted, although not significant. 4. On Visit 2, after prolonged TENS, the percentage of normal slow waves positively correlated to sympathovagal balance; and the percentage of slow wave coupling inversely correlated with the frequency of abdominal pain.

Improved responses of gastric slow waves have been described with gastric electrical stimulation (GES) of the serosal or muscular layers with use of implantable devices in animal and clinical studies (40-43), including vagotomised animals (44). Our clinical data extend the previous studies by demonstrating that an external electrostimulation protocol can also improve GI functioning and symptoms through neuromuscular stimulation in SSc patients.

Importantly, significant improvements in awakening from abdominal pain and small improvements in abdominal

bloating were also demonstrated after prolonged TENS treatments. Small improvements in average SF-36 body pain and vitality domain scores were also noted. Significantly improved scores in total GI symptoms and physical functioning domain were previously reported by our group (23). Our previous study demonstrated an improvement in sympathovagal balance and improved total GI symptoms scores from the GIDQ after prolonged TENS in SSc patients (14, 23). The current study demonstrates an improvement in GMA and a synchronisation of the GMA to sympathovagal tone with TENS. This dynamic shift in neurogastrointestinal coordination in SSc supports the potential for GI entrainment and improved function.

Significant fluctuations in plasma levels of VIP, motilin and IL-6 were noted in response to acute and prolonged TENS applications, presumably in part by modulation of the autonomic nervous system. Elevated VIP levels in plasma, (12, 14) and GI tissue mediators (45) have been reported in SSc patients. Elevated plasma VIP levels have been associated with gastroesophageal reflux disease (46), although other studies have noted the lack of association between plasma GI peptide levels and symptoms in SSc patients (47). Elevated plasma motilin levels have also been reported in SSc patients, (45, 47).

Of great interest, plasma levels of IL-6 significantly increased with acute TENS and significantly decreased after prolonged TENS treatment, compared to baseline values. In our study, decreasing plasma IL-6 levels were inversely associated with increasing frequencies of gastric slow waves and gastric wave coupling. We have selected measuring IL-6 plasma levels, as this critical cytokine and monocyte chemoattractant-1 mRNA have been associated with intestinal hypomotility and inflammation in a sepsis animal model (49). In addition, it is known that in SSc patients there is an increased expression of profibrotic mediators and cytokines associated with severe GI fibrosis and hypomotility. Immunohistochemical examination of gastric tissues from SSc patients found myofibroblasts, increased deposition of collagen, and increased tis-

sue expression of transforming growth factor-beta, connective tissue growth factor and endothelin-1 (48).

This study shows for the first time the effect of acute and prolonged TENS on GMA and plasma levels of VIP, motilin and IL-6 in SSc patients. It will be important to determine if early TENS can impact the development of gastric muscular atrophy seen in SSc or other conditions of dysmotility. Also, the physiologic and long term consequences of modulation of the release of gastric peptides, neurotransmitters and/or vasoactive and inflammatory mediators by electrostimulation and its effects on functioning need to be elucidated. It will most important to determine if improvements in functioning will result in an improvement in GI related symptoms. Many modalities show efficacy short term, but become less effective over time. The advantage of electrostimulation and physiologic normalisation is the potential for long term improvement. This becomes especially important as medical treatments such as proton pump inhibitors (PPI) for GERD initially demonstrated great promise but have not shown long term benefit when formally tested (50). Pakozdi *et al.* also demonstrated a high frequency of adverse events on PPI therapy, and hopefully a non-pharmacologic treatment might be better tolerated. Expanded studies with larger patient numbers will be needed to determine the long term efficacy of TENS and if clinically responsive SSc subsets and treatment conditions will optimise its effects on GI function and symptoms in SSc GI dysmotility.

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APPENDIX

1. Explanation of the four channel surface electrogastrography (EGG) and the measured gastric myoelectrical activity (GMA).

The gastric slow wave determines the frequency and propagation of gastric contractions. The gastric slow wave propagates from the corpus of the stomach (channels 1 and 2) distally towards the pylorus (channels 3 and 4), maintaining a basal rhythm of 2–4 cpm. The spikes (superimposed on slow waves) determine the presence or absence of contractions by electromechanical coupling (1;2). According to the frequencies, gastric slow waves are classified as bradygastria (0.5–2 cycles/min, cpm), normal slow waves (2–4 cpm), tachygastria (4–9 cpm), or arrhythmia (absence of a dominant rhythm).

The recorded EGG data are converted from analogue to digital with a sampling frequency of 1Hz online and stored on an IBM-compatible computer. Computerised spectral analyses are then applied to derive the following parameters from the 4-channel EGG: 1) dominant frequency of the EGG (DF) which reflect the frequency of the gastric slow wave, 2) dominant power of the EGG (DP) reflecting slow wave amplitude, 3) % normal slow waves, 4) % bradygastria, 5) % tachygastria, 6) % gastric arrhythmia and 7) % slow wave coupling, reflecting the coordination of slow waves between two gastric regions. The percentage of slow wave coupling is calculated between any two channels. The percentage of average slow wave coupling which represents the average of percentages of slow wave coupling among all possible channel pairs (n=7) can also be calculated (1-4).

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2. Education of use of the TENS units for home use by the patients

Two-channel electrical stimulation was performed via two lead wires of a TENS device (Vital EMS T.M.; Vitalityweb.com). The patients were loaned the same TENS unit models that were used during the study visit to perform the prolonged TENS protocol. The patients were trained at the end of V1 by "H.S.". The patients were instructed in correct lead placement bilaterally at GI acupoints PC6 and ST36 (one channel connected to the bilateral ST36 (Zusanli) points and the other channel to the bilateral PC6 (Neiguan) points - Fig. 1). The patients were then allowed to place the leads independently to confirm correct lead placement. The patients were also provided with a protocol that contained written instructions and an illustration of the acupoints with lead placement. The patients were provided with a 4 lead TENS unit along with a replacement 9 volt battery to take home.

The parameters for TENS were: 25Hz, 2 sec. on and 2–10 mA (according to the tolerance of each patient). The unit was preset internally so that the patient only needed instruction on how to adjust the external TENS dials to patient tolerability. The TENS units were set to deliver through both lead pairs. The patients were instructed to use the TENS units for 30 minutes, twice daily (before breakfast and before evening meal). To monitor patient compliance, patients were instructed to fill in a daily diary with questions to assess the use and tolerability of the TENS units. We also followed up the patients by phone after the first week to ensure compliance and correct use of the TENS units. All patients reported compliance $\geq 90\%$ and that the procedure was well tolerated.



Fig. 1. Placement of the TENS electrode leads at GI acupoints PC6 and ST36.

3. Supplemental scores from completed instruments.

Appendix Table I: SF-36 Domain and Summary Scores from Visit 1 and Visit 2

Visit			PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
V1	Average		27.78	35.44	38.32	38.06	39.17	42.77	39.85	47.37	31.05	48.05
	SE		2.13	2.53	1.94	2.7	2.24	2.59	3.74	2.96	1.57	2.93
	Range		15-44	27-56	25-51	17-55	23-58	19-57	23-55	18-64	21-42	33-65
V2	Average		29.75	35.86	40.20	35.05	43.07	41.81	40.47	49.51	31.41	49.38
	SE		1.97	2.77	2.58	2.45	2.41	3.46	3.26	2.81	1.62	3.06
	Range		15-38	27-56	19-62	17-55	23-60	13-57	23-55	18-64	22-41	20-64

Average $\pm$ SE scores and domain score ranges from the SF-36 instruments from visits 1 (V1) and 2 (V2). The scores from each domain are shown. PF: physical functioning; RP: role-physical; BP: body pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; and MH: mental health. The scores from the physical component summary (PCS) and mental component summary (MCS) are also shown.

Appendix Table II: Medsger Severity Index

	MSS Total	MSS General	MSS Skin	MSS Gastrointestinal
Average	7.76	0.53	1.23	1.35
SE	0.82	0.21	0.11	0.21
Score range	2-14	0-3	1-2	0-3

Average $\pm$ SE scores and ranges of scores from the Medsger Severity Score Index.

Appendix Table III: GIDQ scores by patients with systemic sclerosis.

GIDQ #	GI Symptoms	% Present by Self Report	GIDQ #	GI Related QOL ITEMS	Average Score $\pm$ SE (Range)
1	Liquids	23%	36	How certain to manage symptoms	65 $\pm$ 8.2 (0-100)
2	Solids	53%	37	Interest in learning about GI	87 $\pm$ 5.4 (0-100)
3	Hoarse	47%	38	Concerned about GI symptoms	71 $\pm$ 8.8 (0-100)
4	Reflux	76%	39	Longer to complete tasks	36 $\pm$ 7.4 (0-100)
5	Chest pain	41%	40	Rate ability to control pain	64 $\pm$ 7 (0-100)
6	On meds ?	94%	41	Feel fatigue	53 $\pm$ 6.7 (6-100)
7	Abd bloating	88%	42	How certain to manage fatigue	62 $\pm$ 8.3 (0-100)
8	Tight clothes	53%	43	Interfere with daily activities	23 $\pm$ 4.3 (0-50)
9	Abdominal distention	29%	44	Rate mental and physical stress	39 $\pm$ 7.5 (0-100)
10	Early satiety	53%	45	How effective is coping	71 $\pm$ 6.4 (0-100)
11	Abdominal pain	47%	46	Limited work on job	27 $\pm$ 8.9 (0-100)
14	Nausea	53%	47	Limited social life	30 $\pm$ 6.6 (0-100)
13	Vomiting	17%	48	Rate disease severity based on QOL (Severity: None to very severe)	44 $\pm$ 5 (0-78)
15	Diarrhoea	29%			
16	Constipation	41%			
17	Diarrhoea/Constipation	12%			
18	Bulky, foul smelling stools	12%			
19	Hard stools	41%			
20	Incomplete bowel move	65%			
21	Rectal bleed	6%			
22	Rectal fullness	47%			
23	Incont stool	23%			
26	Hospitalised last 6 mo	6%			
	Hospitalised for GI ever	23%			
27	Awakened by pain	21%			
32	Change occupation	11%			
33	Change normal activities	29%			

The Gastrointestinal Dysmotility Questionnaire (GIDQ) was developed to assess the presence, frequency and intensity of GI related symptoms. Part 1 refers to GI related symptoms and Part 2 refers to GI related quality of life (QOL). Patients responded to GIDQ items by answering yes or no, or by VAS scoring. The table displays scores of selected items from the GIDQ, as noted below.
Esophageal: 1. Do you have difficulty swallowing liquids? 2. Do you have difficulty swallowing solid food? 3. Do you have any hoarseness? 4. Have you had any heartburn or acid reflux? 5. Have you had any pain or pressure behind the chest bone? 6. Are you taking any medication(s) as treatment for any of the above mentioned problems? Stomach and Small Intestine: 7. Do you experience a sensation of gas and/or bloating in the abdomen? 8. Have you increased a clothes size or adjusted your clothes for this problem? 9. Do you feel discomfort in your abdomen every day? 10. Do you have a sensation of fullness early in the meal (early satiety)?

11. Do you have abdominal pain? If YES to question 11, please indicate the frequency of pain by the number of days a week that you had pain on the scales provided below VAS (0–7 days). 12. How many days last week did you experience abdominal pain? 13. Have you been bothered by vomiting? a. How many days last week did you experience vomiting? 14. Have you been bothered by nausea? a. How many days last week did you experience nausea? **Large Intestine and Anorectal Symptoms:** In the last week... 15. Have you been bothered by diarrhoea? a. How many days last week did you experience diarrhoea? 16. Have you been bothered by constipation? a. How many days last week did you experience constipation? 17. Have you been having both diarrhea alternating with constipation? a. How many days last week did you experience diarrhoea/constipation? 18. Do you have bulky or foul smelling stools? a. How many days last week did you have foul smelling stools? 19. Have you been bothered by hard stools? a. How many days last week did you experience hard stools? 20. Do you have a feeling of incomplete bowel movement? 21. Do you have bleeding per rectum because of straining? a. How many days last week did you experience bleeding because of straining? 22. Do you have a sensation of fullness in the rectum after a bowel movement? 23. Have you had stool incontinence (*i.e.* have you soiled your pants?), a. How many days last week did you experience fecal incontinence? 24. Have you been bothered by black, tarry stools? How often do you experience black, tarry stools? 2. Daily activities refer to requirements of daily living, for example, maintenance or upkeep of your place of residence, gardening, shopping, and yard work 25. Have you lost 20 pounds, or greater than 15% of your usual weight in the past 6 months? 26. Have you

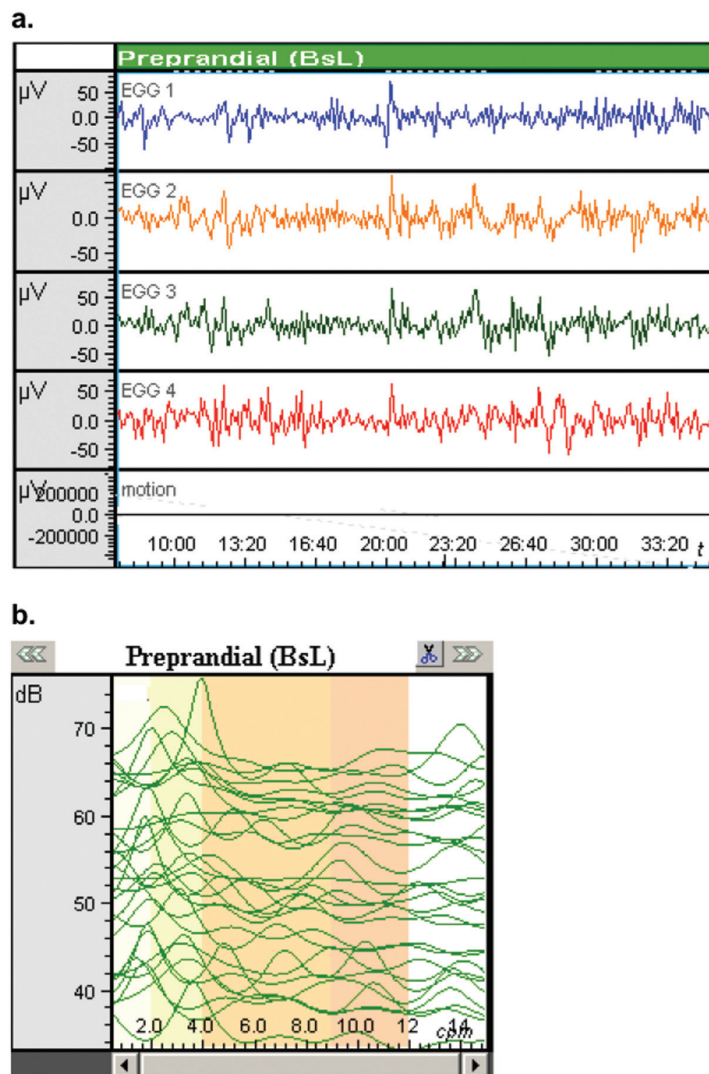


Fig. 2. Representative EGG tracing and power spectral analysis images of an SSc patient during V1. **a.** baseline (BsL) recording showing irregular EGG signal and uncoordinated gastric slow waves; **b.** Generated power spectral analysis confirming gastric dysrhythmias in channel 1.

had any hospitalisation related to GI problems in past 6 months? 27. a. If yes to Question-26, How many hospitalisations and what were the discharge diagnoses, if known? 28. Have you ever received, a) Total parental Nutrition (TPN), where the doctors rested your gut by feeding you by venous infusion in the past 6 months? b) Have you ever been on TPN? 29. a) Have you awakened in the middle of the night by GI pain in past 4 weeks? Last 7 days? b) How often in the last week have you awakened in the middle of the

night because of GI pain? 30. Have you used non-prescription medications, herbal therapies or alternative therapies (Acupuncture, Hypnotherapy, Yoga, etc.) to relieve your GI symptoms in past 6 months? If YES to Question-30 then please list the non-prescription meds and alternative therapies and their effectiveness (0-100) to relieve your symptoms.31. Do you have a history of peptic ulcer disease diagnosed by a physician? 32. Have you had to change occupations because of your GI symptoms? 33. Have you had to change any normal daily errand or task you usually perform at home or work because of GI symptoms?

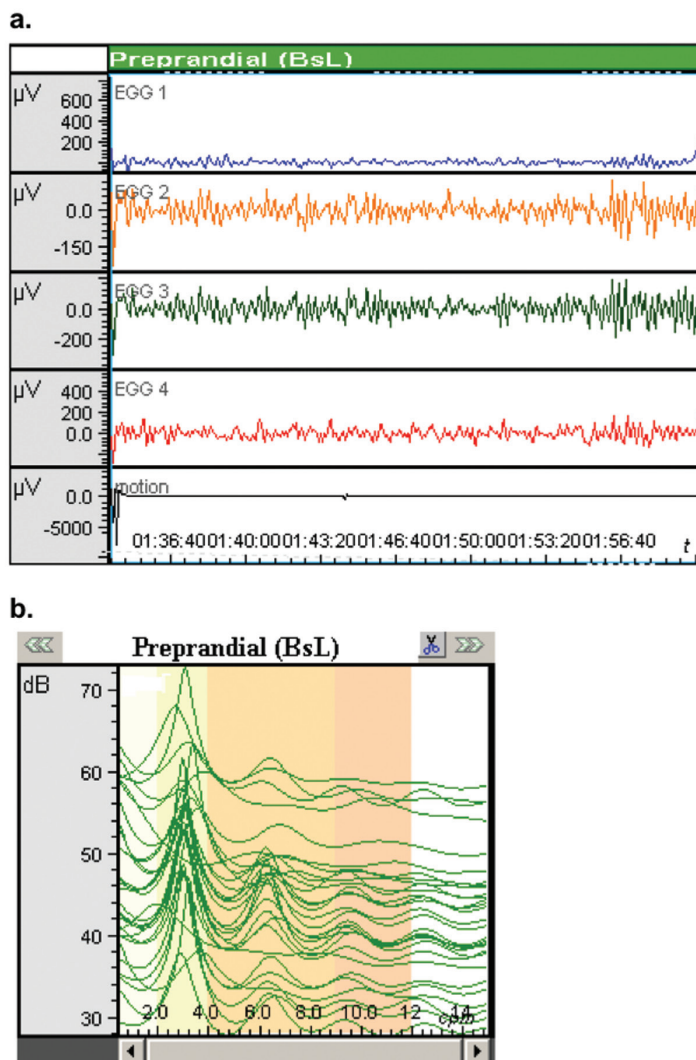


Fig. 3. BsL recording of the same SSc patient during V2, after 2 weeks of home TENS self-treatment. **a.** BsL recording showing regular EGG signals; **b.** Generated power spectrum image confirming improvement of normal slow waves in channel 1.

If YES to questions 32 or 33, please list the changes. Please place a mark on the line to indicate your level of GI involvement in the last week to the following (VAS 0–100). 34. How much discomfort have you had because of abdominal pain? 35. How much discomfort have you had because of bloating? 36. How certain are you that you can manage your GI symptoms so that you can do the things you enjoy doing? 37. What is your level of interest in learning more about your GI problems? 38. Are you concerned with your GI problems? 39. Does it take longer for you to complete tasks with your GI problems? 40. How would you rate your ability to control your pain due to GI problems? 41. Do you feel fatigued at times? 42. How certain are you that you can manage your fatigue? 43. In the past week how much have your GI problems interfered with your daily activities? 44. How would you rate mental or physical stress that have an affect on your GI problems? 45. How effective are you coping with your GI problems? 46. Have your GI problems limited your work at your place of employment? 47. Has your GI problems limited your social life? 48. Overall, considering pain, discomfort, limitations in your daily life and other changes in your body and life; how severe would you rate your disease today? Thank you for participating in this project.

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