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**Title:** A feasibility study exploring measures of autonomic function in patients with failed back surgery syndrome undergoing spinal cord stimulation

**Running title:** Spinal cord stimulation and autonomic function

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**ABSTRACT**

**Objectives**
Failed back surgery syndrome (FBSS) is associated with impaired autonomic tone, characterised by sympathetic prevalence and vagal withdrawal. Although spinal cord stimulation (SCS) alleviates pain in FBSS, there is limited research investigating how SCS impacts measures of autonomic function. This was a prospective, open-label, feasibility study exploring measures of autonomic function in patients with FBSS receiving SCS therapy.

**Methods**
Fourteen patients with FBSS were recruited for baseline measurements and underwent a trial of 10 kHz SCS. There were three failed trials, resulting in the remaining 11 participants receiving a fully implanted 10 kHz SCS system. One participant requested an explant, resulting in 10 participants completing both baseline and follow-up (3-6 months after SCS implant) measurements. Autonomic function was assessed using time- and frequency-domain heart rate variability (HRV), baroreceptor reflex sensitivity (BRS) and muscle sympathetic nerve activity (MSNA) using microneurography. As this was a feasibility study, most of the analysis was descriptive. However, paired t-tests and Wilcoxon signed-rank tests tested for differences between baseline and follow-up.

**Results**
In the whole (n = 14) and final (n = 10) samples, there was between-participant variation in baseline and follow-up measures. This, combined with a small sample, likely contributed to finding no statistically significant differences in any of the measures between baseline and follow-up. However, plotting baseline and follow-up scores for individual participants revealed that baseline values for those who showed increases in MSNA frequency, RMSSD, pRR50, total power and up BRS between baseline and follow-up, had distinct clustering of baseline values compared to those who showed decreases in these measures.

**Conclusion**
Findings from this feasibility study will aid with informing hypotheses for future research. A key aspect that should be considered in future research concerns exploring the role of baseline measures of autonomic function in influencing change in autonomic function with SCS therapy.

**KEY WORDS**
Failed back surgery syndrome (FBSS)
Autonomic function
Spinal cord stimulation (SCS)
Muscle sympathetic nerve activity (MSNA)
Baroreceptor reflex sensitivity (BRS)
Heart rate variability (HRV)

## INTRODUCTION

Spinal cord stimulation (SCS) is a NICE approved treatment for chronic pain of neuropathic origin (NICE TA159 and NICE MTG41). SCS reduces pain in a number of chronic pain conditions, including chronic axial back pain [1,2] with/without leg pain [3–8], failed back surgery syndrome (FBSS) [9], fibromyalgia [10] and complex regional pain syndrome (CRPS) [11]. Deteriorations in measures associated with autonomic function also occur in chronic pain conditions. For instance, heart rate variability (HRV), a collective term for a panel of measures considered to reflect autonomic function, was reduced in individuals with chronic neck pain [12], abdominal pain [13], CRPS [14] and chronic pelvic pain [15]. Additionally, abnormalities such as longer latencies in sympathetic skin response [16] have been observed in FBSS, with positive correlations between sympathetic skin response and degree of pain-related disability [17].

In chronic pain conditions, reductions in pain occur with improvements in measures of HRV. In individuals with lower back or leg pain, treatment by epidural injection of local anaesthetic and corticosteroid was associated with pain relief and increases in HRV [18]. In a sample of 22 individuals with FBSS, SCS significantly improved parameters associated with autonomic function, with measures suggesting a shift towards parasympathetic influence [19]. More recently, active SCS was associated with decreases in heart rate and respiration [20]. However, contrasting findings have also emerged. SCS was linked to heightened heart rate and reductions in high frequency (HF) HRV [21], suggesting a reduction in parasympathetic activity. The discrepancy between these SCS studies may be due to the use of different SCS systems (e.g. 10 kHz SCS, tonic SCS) in different chronic pain conditions (e.g. FBSS, CRPS).

Previous research investigating the autonomic effects of SCS in chronic pain has typically derived heart rate and its variability (HRV) [19–21]. Although insight into changes in parasympathetic activity can be gained from HRV, they provide indirect assessments of autonomic function and generate limited information about how sympathetic activity is altered. As SCS is thought to modulate spinal circuits which in turn regulate sympathetic activity [22,23], obtaining a direct measure of sympathetic activity is crucial for understanding how autonomic function is impacted in chronic pain conditions and with SCS therapy. This can be achieved by using microneurography to directly measure muscle sympathetic nerve activity (MSNA) [24,25]. Indeed, in research that investigates autonomic function in patients with chronic pain, there are increasing calls for these studies to incorporate microneurography [26]. Experimentally induced pain has been shown to increase MSNA activity [27] and there is emerging evidence of a linear relationship between MSNA burst rate and pain intensity [28].

The baroreceptor reflex is a key homeostatic mechanism that regulates blood pressure changes by controlling heart rate and peripheral resistance [29]. The baroreceptor reflex can be quantified by assessing baroreceptor reflex sensitivity (BRS). BRS is a predictor of mortality [30,31] and has been shown to be modulated by other forms of neuromodulation [32,33]. With regards to pain, there is evidence to support the view that baroreflex function modulates pain perception, where the occurrence, directionality and efficacy of BRS on pain perception can be influenced by a range of factors [34]. There is also increasing clinical evidence of the contribution of baroreceptor function to the aetiology and maintenance of chronic pain conditions (see [34] for a review). In addition, cardiac baroreflex function is thought to be inversely correlated with pain intensity in patients with fibromyalgia [28]. Despite this research, to our knowledge, studies investigating the autonomic effects of SCS have not yet explored whether SCS influences baroreflex function, as indexed by BRS.

This feasibility study explored measures of MSNA, HRV and BRS in individuals with FBSS who were scheduled to receive 10 kHz SCS. We were particularly interested in exploring the viability of recording and quantifying MSNA, given its advantage over HRV and its potential use in larger, future trials. This study was therefore exploratory and not hypothesis driven. It was hoped that findings from this study

would aid with informing the design, research questions, and primary and secondary outcomes for future research.

## METHODS

### Ethical approval

This was a prospective, single centre, open-label, feasibility study undertaken in the Leeds Teaching Hospitals NHS Trust, UK, between April 2015 and December 2017. The study was conducted according to the standards of International Conference on Harmonization Good Clinical Practice Guideline, declaration of Helsinki, Research Ethics Committee regulations, EU Clinical Trial Directive and Local NHS Trust Research Office policies and procedures. Research ethics committee approval was granted by the NHS Research Ethics Committee Yorkshire and The Humber - Sheffield.

### Participants

Recruited patients fulfilled the inclusion criteria: 1) male or female aged ≥18 years; 2) diagnosed with FBSS with persistent low back pain, with or without radiculopathy, for a minimum of 6 months post spinal surgery.

The exclusion criteria included: 1) postural hypotension; 2) bradycardia; 3) cardiac arrhythmia; 4) a permanent pacemaker; 5) diabetic neuropathy or neuropathy involving the common peroneal nerve, including nerve entrapment syndromes; 6) neurologic or psychiatric conditions; 7) a history of alcoholism or drug abuse within the last two years; 8) concomitantly taking beta-blockers or alpha-blockers. Individuals taking statins were not excluded from the study provided they did not commence or change dose over the duration of the study.

### Procedure

To standardise according to variations in circadian rhythm, all study visits were conducted between 13:00 and 17:00. Participants were asked to abstain from caffeine, alcohol, nicotine and strenuous exercise 12 hours before study commencement. Participants attended on two occasions: prior to SCS implant (baseline) and 3-6 months following fully implanted 10 kHz SCS (follow-up). The protocol was the same across participants and study visits (see Figure 1 for a summary of the study schedule).

At the beginning of each visit, participant height and weight were obtained. Physiological equipment that continuously recorded heart rate, blood pressure, muscle sympathetic nerve activity (MSNA) and respiration were then attached. Participants reclined semi-supine on a couch for the duration of the visits.

For MSNA, the peroneal nerve was identified by palpation. Following confirmation of the peroneal nerve, two tungsten microelectrodes (FHC Inc., USA) were inserted percutaneously. The microelectrodes were 35 mm in length with a diameter of 200 μm tapering to a tip. The recording microelectrode (epoxy insulated with an impedance of 0.3 ± 0.6 MΩ) was inserted into the peroneal nerve, and the reference microelectrode was inserted into subcutaneous tissue 1-2 cm away from the recording electrode. To aid with identifying MSNA units, participants undertook one of two cardiovascular tests: cold pressor test (submerging the left hand into ice water for two minutes); or the isometric hand grip test (squeezing a handgrip at 50% maximum voluntary contraction for two minutes). If no potential units could be identified whilst the tests were undertaken, the recording electrode was manipulated in the nerve up until 45 minutes had passed. After this time, the needle was not moved until the end of the visit.

Following the MSNA set-up, a 10-minute recording of the physiological measures was obtained while participants were at rest. All equipment was subsequently detached from participants and the study visit completed.

INSERT FIGURE 1 HERE

**10 kHz SCS**

For 10 kHz SCS, percutaneous leads were placed in the dorsal epidural space attached to either an external stimulator during the initial temporary trial or a rechargeable implantable pulse generator subcutaneously implanted in the chest wall or buttock for the fully implanted 10 kHz SCS system. Based on established practice [1], electrode leads were placed between T8 and T11, and the following stimulation was delivered: frequency = 10 kHz, pulse width = 30 μs and current = 1-5 mA. SCS stimulation parameters were modified based on patient feedback in order to elicit the most effective pain relief.

**Measurements**

Heart rate was recorded by a three-lead electrocardiogram (ECG) with three Ag-AgCl surface electrodes placed on the chest and sampled at 2 kHz. Continuous blood pressure was recorded via finger pulse plethysmography (Finometer; Finapres Medical System, Netherlands), sampled at 400 Hz. Continuous blood pressure recordings were obtained for the purpose of deriving baroreceptor reflex sensitivity (BRS). MSNA was recorded as previously described [24,25]. In brief: sampled at 10 kHz and a 700-2000 Hz band pass filter was applied. Respiration was recorded via a strain-gauge transducer (Pneumotrace, UFI, CA, USA) placed around the chest and sampled at 0.4 kHz. Although participants breathed spontaneously, their respiration rate was carefully monitored to ensure respiration rate did not drop below 10 breaths per minute. All data were continuously recorded in LabChart 8 (AD Instruments).

**Data analysis**

Time-domain HRV, frequency-domain HRV, sequence BRS, MSNA frequency and MSNA incidence were derived for the final five minutes of each recording (see Table 1 for a summary). Change (Δ) between baseline and follow-up was calculated for all measures.

**Time-domain HRV**

Five time-domain HRV parameters were derived (in LabChart 8): mean RR interval; standard deviation of successive RR intervals (SDRR); difference between the maximum and minimum RR intervals (Δ RR); square root of the mean of the squared differences between adjacent RR intervals (RMSSD); and percentage of the number of RR intervals larger than 50 ms (pRR50). Δ RR and SDRR are thought to reflect overall variability in heart rate, and RMSSD and pRR50 are thought to represent parasympathetic influence on the heart [35].

**Frequency-domain HRV**

Frequency-domain HRV parameters (in LabChart 8) included: power in the low frequency (LF) component, detected at 0.04-0.15 Hz; power in the high frequency (HF) component, detected at 0.15-0.40 Hz; total power (0.04-0.40 Hz); normalised values for LF (nuLF) and HF power (nuHF) and the ratio of LF to HF power (LF/HF ratio). Currently, there is controversy concerning the physiological interpretation of LF power. Previously, it was proposed that LF power provided a means to indirectly evaluate the ability of the autonomic nervous system to modulate both sympathetic and parasympathetic outflow [35]. However, more recent propositions suggest that LF power may reflect baroreflex modulation of autonomic outflow rather than cardiac sympathetic innervation [36–39]. In contrast, the HF component of HRV is thought to be associated with parasympathetic activity [35].

**Spontaneous sequence BRS**

Spontaneous BRS was non-invasively derived via the sequence method, in which ‘up’ and ‘down’ sequences were identified (in LabChart 8). ‘Up’ sequences comprised of three or more consecutive cardiac cycles for which there was a sequential rise in both systolic blood pressure (SBP, ≥ 1 mmHg) and RR interval (≥ 2 ms). ‘Down’ sequences consisted of three or more cardiac cycles for which there was a sequential fall in SBP and RR interval. In Excel 2013, BRS values were derived by plotting RR

interval against SBP and calculating the slope of the line fitted through the data points. The slope of the line was used as an index of BRS: the steeper the slope, the greater the BRS [40].

**Muscle sympathetic nerve activity (MSNA)**

MSNA analysis was performed in Spike2 software (CED). Nerve and blood pressure traces were exported from LabChart 8 in a single text file and imported into Spike2. Confirmed MSNA units: occurred in diastole; increased in firing with increases in blood pressure; had a higher firing rate during the second half compared to the first half of the tests; and the shape and rate of the units did not change during the stroking of the upper foot or when superimposed (Corel Draw, Version 6). Frequency (per minute) was calculated by counting all single units that occurred in the final five-minutes of the 10-minute recording divided by the condition's duration. MSNA incidence (number of units per 100 heart beats) was also derived to limit the effect of any changes in heart rate. This involved dividing MSNA frequency by mean heart rate and multiplying by 100.

INSERT TABLE 1 HERE

**Statistical analysis**

This was a feasibility study that aimed to explore the viability of obtaining measures that are associated with autonomic function in patients with FBSS that were awaiting 10 kHz SCS therapy. To that end, the focus of the statistical analyses was primarily descriptive. This entailed generating descriptive statistics (mean ± standard deviation [SD], median, minimum and maximum) for all measures of autonomic function at both baseline and follow-up. It was hoped this would aid with generating the data needed to help future research to work towards developing an autonomic profile of patients with FBSS.

To aid with designing future research, particularly relating to sample size calculations, paired sample t-tests (or Wilcoxon signed-rank tests for non-normally distributed data) explored differences in measures associated with autonomic function between baseline and follow-up. For estimates of effect size, Cohen's d was calculated for paired sample t-tests and r was calculated for Wilcoxon signed-rank tests. Normality was ascertained via the Shapiro-Wilk test. Paired sample t-tests and Wilcoxon signed-rank tests were two-tailed and performed in SPSS (version 25). As 16 measures of autonomic function were derived, the alpha level was adjusted to 0.003 (0.05/16).

## RESULTS

### Participant progression and characteristics

Fourteen patients with FBSS were recruited (n = 7 males, 7 females; mean ± SD age: 52 ± 8 years; age range: 43-68 years, see Table 2

INSERT TABLE 2 HERE

). None of the patients had only axial back pain. Three participants failed the SCS trial (i.e. obtained <50% pain relief), resulting in 11 participants receiving a fully implanted 10 kHz SCS system. Prior to the follow-up visit, one participant requested explant of the system due to finding the stimulation unpleasant. This resulted in 10 participants completing the follow-up visit. Figure 2 summarises participant progression through the study schedule.

INSERT FIGURE 2 HERE

The final sample comprised the 10 participants who completed the baseline and follow-up visits. Table 2 provides a summary of the characteristics of the whole sample (n = 14 participants who completed the baseline visit) and the final sample (n = 10 participants who completed the baseline and follow-up visits).

INSERT TABLE 2 HERE

### MSNA at baseline and follow-up

There were confirmed MSNA units in 11 participants for whom baseline data were captured. MSNA units in the follow-up visit were confirmed in six of these 11 participants. Figure 3 provides an example cold pressor test trace from which individual action potentials were identified and overlaid to confirm a single MSNA unit. Supplementary Figures 1-16 show the cold pressor/hand grip traces, putative individual action potentials and overlaid action potentials for the remaining confirmed MSNA units in the baseline and follow-up visits.

INSERT FIGURE 3 HERE

In the whole sample at baseline (n = 11), mean ± SD MSNA frequency and MSNA incidence were 4.10 ± 1.98 units/minute and 6.39 ± 3.39 units/100 heartbeats respectively (see Table 3). Values ranged from 0.80 to 6.85 units/minute for MSNA frequency and 0.96 to 12.12 units/100 heart beats for MSNA incidence.

As the final sample was small (n = 6), statistically testing for differences in MSNA frequency and incidence between baseline and follow-up was likely to be under powered. Indeed, in the final sample, the decrease in MSNA frequency from 3.43 ± 1.34 units/minute at baseline to 2.77 ± 1.56 units/minute at follow-up was not statistically significant ($p > 0.05$, see Table 3). Similarly, the decrease in MSNA incidence from 5.13 ± 1.72 units/100 heart beats at baseline to 4.19 ± 2.88 units/100 heart beats at follow-up did not reach statistical significance ($p > 0.05$, see Table 3).

INSERT TABLE 3 HERE

As MSNA frequency and MSNA incidence appeared to vary between participants at baseline, we plotted individual participants to graphically explore whether there was any clustering of values at this visit. Indeed, of the four participants in whom MSNA frequency decreased between baseline and follow-up, three participants had the three highest MSNA frequency values at baseline (see Figure 4a).

Interestingly, the fourth participant had the lowest MSNA frequency at baseline of the sample, which subsequently decreased by 0.4 units/minute.

For MSNA incidence, there seemed to be little evidence of clustering of values at baseline (see Figure 4b).

INSERT FIGURE 4 HERE

**Time-domain HRV at baseline and follow-up**

In the whole sample, there was variability between participants in the time-domain HRV measures at baseline (see Table 4). Perhaps due to the small sample size in the final sample, there were no statistically significant differences between baseline and follow-up in any of the time-domain HRV measures (see Table 4).

INSERT TABLE 4 HERE

Clustering in baseline RMSSD values was observed (see Figure 5c). Indeed, for participants who demonstrated increases in RMSSD (n = 4), baseline values clustered between 11.51 ms and 22.68 ms (mean ± SD: 18.35 ± 5.39 ms). For participants who showed decreases in RMSSD between the two timepoints (n = 6), they had values lower or greater than this range (min: 4.09 ms; max: 65.56 ms; mean ± SD: 34.23 ± 25.17 ms). The mean ± SD change in RMSSD between baseline and follow-up was 8.62 ± 3.07 ms and -15.03 ± 12.30 ms for the two groups respectively. Interestingly, baseline RMSSD values for three of the four participants who did not continue to the follow-up visit were clustered amongst baseline RMSSD values for participants who showed increases between baseline and follow-up.

For participants who showed increases in pRR50 at follow-up (n = 3, see Figure 5d), values clustered between 0% and 4.72% (mean ± SD: 2.38 ± 2.36%). For participants who showed decreases in pRR50, baseline values were greater than this range (min: 9.54%; max: 44.44%; mean ± SD: 25.53 ± 15.48%, n = 4). Two participants, both of which had baseline values of 0%, showed no change between the two timepoints. The mean ± SD change between baseline and follow-up for participants who showed increases in pRR50 was 2.51 ± 0.36%. For those who showed decreases in pRR50 between the two timepoints, the mean ± SD change was -18.29 ± 10.46%. For the four participants who did not complete the follow-up visit, baseline values were within the clustering of those who either showed increases or no change in pRR50 at follow-up.

Evidence of clustering for mean RR interval (see Figure 5a), SDRR (see Figure 5b) and Δ RR interval (see Figure 5e) were less evident.

INSERT FIGURE 5 HERE

**Frequency-domain HRV at baseline and follow-up**

In the whole sample, there was variability between participants in the frequency-domain HRV measures at baseline (see Table 5). Similar to the time-domain HRV analysis in the final sample, there were no statistically significant differences between baseline and follow-up in any of the frequency-domain HRV measures (see Table 5).

INSERT TABLE 5 HERE

There was some evidence of clustering at baseline in total power (see Figure 6a) that was comparable to RMSSD. Indeed, for the four participants who demonstrated increases in total power, baseline values clustered between 320.70 $ms^2$ and 881.10 $ms^2$ (mean ± SD: 666.78 ± 261.41 $ms^2$). For the remaining participants who showed decreases in total power between the two timepoints, they had values lower or greater than this range (min: 201.20 $ms^2$; max: 4964.80 $ms^2$; mean ± SD: ± 25.17 $ms^2$). The mean ± SD change in total power between baseline and follow-up was 438.65 ± 260.93 $ms^2$ and -1121.26 ± 909.94 $ms^2$ for the two groups respectively.

Clustering patterns for LF power (see Figure 6b), HF power (see Figure 6c), nuLF (see Figure 6d), nuHF (see Figure 6e) and LF/HF ratio (see Figure 6f) were less clear.

INSERT FIGURE 6 HERE

**BRS at baseline and follow-up**

Due to a poor continuous blood pressure trace for one participant, it was not possible to reliably quantify BRS. This resulted in BRS measures for 13 participants in the whole sample and 10 in the final sample. As depicted in Table 6, up, down and mean BRS varied between participants in both the whole and final samples. Statistical analysis comparing baseline to follow-up values revealed no statistically significant differences in any of the BRS measures (see Table 6 for a summary).

INSERT TABLE 6 HERE

There was some evidence of clustering of baseline up BRS values (see Figure 7a). Indeed, for participants who showed increases in up BRS between baseline and follow-up (n = 5), values clustered between 6.14 ms/mmHg and 7.57 ms/mmHg (mean ± SD: 6.71 ± 0.71 ms/mmHg). For participants who showed decreases in up BRS between the two timepoints (n = 5), they had values lower or greater than this range (min: 2.87 ms/mmHg; max: 23.64 ms/mmHg; mean ± SD: 12.00 ± 8.38 ms/mmHg). The mean ± SD change in up BRS between baseline and follow-up was 4.76 ± 1.87 ms/mmHg and -6.19 ± 4.10 ms/mmHg for the two groups respectively.

For down BRS (see Figure 7b) and mean BRS (see Figure 7b) the clustering patterns were less clear.

INSERT FIGURE 7 HERE

## DISCUSSION

This was a prospective, open-label, feasibility study exploring measures of autonomic function in patients with FBSS receiving SCS therapy. The study was exploratory and not hypothesis driven. Descriptive statistics showed that in the whole (n = 14) and final (n = 10) samples, there was between-participant variation in baseline and follow-up measures. This, combined with a small sample, likely contributed to finding no statistically significant differences in any of the measures between baseline and follow-up. However, plotting baseline and follow-up scores for individual participants revealed that baseline values for those who showed increases in MSNA frequency, RMSSD, pRR50, total power and up BRS between baseline and follow-up, had distinct clustering of baseline values compared to those who showed decreases in these measures. Findings from this feasibility study will aid with design considerations, potential research questions and new hypotheses for future research. An aspect that could be considered in future research relates to the role baseline measures of autonomic function may play in influencing change in autonomic function with SCS therapy.

### MSNA, HRV and BRS in FBSS with SCS

Autonomic dysfunction has been shown to occur in individuals with FBSS [16,17]. Although some participants had attenuated autonomic function in this feasibility study, other participants had MSNA, HRV and BRS values that were consistent with what would be expected in pain-free individuals. Although the focus of this feasibility study was primarily exploratory (generating descriptive statistics), we conducted paired sample t-tests and Wilcoxon signed-rank tests to explore differences in measures associated with autonomic function between baseline and follow-up. Due to the inter-participant variation observed at baseline and follow-up, combined with the small sample size, we were unsurprised to find no statistically significant differences in measures of autonomic function between the two timepoints. Nevertheless, findings from this study should help with generating the data needed that can aid with informing sample size calculations in subsequent research.

Due to controversy with some HRV parameters (particularly the LF component of HRV power, [36–38]), we were interested in exploring how other measures reflecting autonomic function were impacted in FBSS and by SCS. This led to using the microneurography technique to derive MSNA frequency and MSNA incidence. A key advantage of MSNA is its ability to provide a direct assessment of sympathetic nerve activity. We acknowledge that confirmed MSNA units were not possible in all participants, resulting in a small number of confirmed MSNA units and perhaps in turn, insufficient statistical power. However, given that we successfully confirmed MSNA units in this patient cohort, a larger study is warranted in which there are more confirmed MSNA units at baseline and follow-up visits.

Baseline measures of autonomic function have been shown to play an influential role in modulating change in autonomic parameters with other forms of neuromodulation. For example, in healthy volunteers receiving transcutaneous auricular nerve stimulation (tANS), high LF/HF ratios at baseline were associated with decreases in LF/HF ratios during stimulation [33,41]. Furthermore, in healthy volunteers aged ≥55 years, low Δ RR interval and mean BRS at baseline were associated with increases when measured following two weeks of daily tANS [33]. Due to the small sample in the current study and the between-participant variability in baseline and follow-up measures, it was not possible to reliably test whether baseline measures of autonomic function were related to specific changes at SCS follow-up. However, the tentative baseline clustering depicted in baseline MSNA frequency, RMSSD, pRR50, total power and up BRS may point to these measures being associated with specific change patterns with 10 kHz SCS therapy. The hypothesis that baseline measures of autonomic function are associated with change at SCS follow-up should be tested in future research. Of course, this should be tested using a conventional statistical method and include a more specific follow-up time point e.g. 6 months.

**Study limitations and future directions**

Research investigating the efficacy and safety of SCS in chronic pain conditions has typically used measures that evaluate pain, pain-related disability, quality of life (QoL), medication consumption and complications [42–44]. We acknowledge that measures typically collected in SCS studies were not obtained here and are a limitation of the study. To improve the methodology and findings, future research employing measures associated with autonomic function should also collect pain, pain-related disability and QoL data at baseline and follow-up visits via validated means. This could include VAS or NRS scales for pain, the Oswestry Disability Index (ODI) for pain-related disability and the EQ-5D-5L for health-related QoL. Such data would aid with exploring a key research question: do changes in pain correlate with changes in measures reflecting autonomic function? I.e. do those experiencing the greatest pain relief with SCS also experience the greatest improvements in measures associated with autonomic function?

SCS screening trials are widely used to determine whether a patient should receive a fully implanted SCS system. Pain relief of at least 50% is usually defined as a successful SCS trial [45]. In our pilot study there were three failed trials (reporting <50% pain relief). Upon inspection of their baseline measures, all three had relatively high LF/HF ratios: 11.42, 7.15 and 3.49 respectively. An MSNA unit was confirmed in one of these participants with MSNA frequency and MSNA incidence being high: 6.85 units/min and 12.12 units/100 heartbeats respectively. This raises the possibility that heightened sympathetic tone at baseline may hinder the ability of participants to assess the effectiveness of the SCS screening trial. In turn, this questions whether a two-week trial is long enough for autonomic function to be restored prior to a fully implanted system, or even whether an SCS screening trial should be conducted at all. Indeed, despite research suggesting that SCS screening trials may have some diagnostic utility, enhanced patient outcomes and greater cost-effectiveness may not be obtained compared to a no trial screening approach [46,47]. Future research should therefore include measurements at the end of the SCS screening trial to explore whether autonomic function is modulated following the trial period and whether changes in autonomic function correlate with the trial's pain-relieving effects. An alternative approach could include reducing sympathetic tone by non-invasive means prior to a SCS trial (e.g. via alpha blockers or tANS) to render the patient more receptive to pain relief and the autonomic effects of SCS therapy.

Despite promising findings, an additional limitation of the study concerns the open-label design and no inclusion of a control group or arm. As a result, it is unclear how changes in measures reflecting autonomic function compare between active SCS and a placebo control. As placebo effects have been suggested to occur with up to 6 months of SCS therapy [48] and 10 kHz SCS is paraesthesia free, future research investigating the impact of SCS on autonomic function and pain should include a placebo SCS control. As 10 kHz SCS therapy was used in this specific patient cohort of FBSS based on current guidance from NICE and best evidence [4], differences in autonomic patterns between SCS modes (e.g. BurstDR, tonic SCS) would be an additional worthwhile avenue for future research. Of course, all of these potential research avenues should be sufficiently powered to correctly detect statistically significant differences. Although the small sample size of the current study is perhaps the main limitation, the findings show that MSNA, HRV and BRS can be measured in this patient cohort and need to be scrutinised in further, larger research.

**Conclusion**

Findings from this feasibility study revealed variation between participants with FBSS in measures of autonomic function at baseline and follow-up. Baseline values for those who showed increases in MSNA frequency, RMSSD, pRR50, total power and up BRS between baseline and follow-up, had clustering of baseline values compared to those who showed decreases in these measures. The relationship between baseline measures of autonomic function and change at SCS follow-up should be tested in future research. This is because baseline autonomic measures may be useful for stratifying

patients prior to receiving SCS. With further appropriately powered research incorporating measures of self-reported pain, pain-related disability and QoL, insight into the relationship between pain relief and autonomic function in the context of SCS therapy may become more understood.

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**TABLES**

Table 1: Summary of measures derived in the study.

| **Measure** | | **Interpretation** |
|---|---|---|
| MSNA | Frequency (units/min) | Muscle sympathetic nerve activity units per minute. |
| | Incidence (units/100 heartbeats) | Muscle sympathetic nerve activity units per 100 heartbeats. |
| Time-domain HRV | Mean RR interval (ms) | Mean RR interval |
| | Δ RR (ms) | Difference between minimum and maximum RR intervals. Overall variability heart rate. |
| | SDRR (ms) | Standard deviation of all normal RR intervals. Overall variability in heart rate. |
| | RMSSD (ms) | The square root of the mean of the squared differences between adjacent RR intervals. Parasympathetic activity. |
| | pRR50 (%) | The percentage of the number of RR intervals larger than 50 ms. Parasympathetic activity. |
| Frequency-domain HRV | Total power ($ms^2$) | Power within the 0.04 – 0.40 Hz frequency band. Overall variability. |
| | LF power ($ms^2$) | Power within the 0.04 to 0.15 Hz frequency band. Combined sympathetic and parasympathetic activity, although disputed. |
| | HF power ($ms^2$) | Power within the 0.15 to 0.4 Hz frequency band. Parasympathetic activity. |
| | nuLF | Normalised LF power. |
| | nuHF | Normalised HF power. |
| | LF/HF | Ratio of LF power to HF power. Autonomic balance, although unclear due to controversy surrounding interpretation of LF power. |
| BRS | Up (ms/mmHg) | Sequential rise in both systolic blood pressure (SBP, ≥ 1 mmHg) and RR interval (≥ 2 ms) for ≥ 3 consecutive cardiac cycles. Parasympathetic activity. |
| | Down (ms/mmHg) | Sequential fall in both systolic blood pressure (SBP, ≥ 1 mmHg) and RR interval (≥ 2 ms) for ≥ 3 consecutive cardiac cycles. Parasympathetic activity. |
| | Mean (ms/mmHg) | The mean of up and down BRS sequences. Parasympathetic activity. |

References: [35–40].

Table 2: Summary of demographic information and baseline characteristics for the whole sample (n = 14) and final sample (n = 10 participants who completed both visits).

| | **Whole sample (n = 14)** | **Final sample (n = 10)** |
|---|---|---|
| Gender (males/females) | 7/7 | 4/6 |
| Age (years) | 52 ± 8 (n = 14) | 52 ± 9 (n = 10) |
| BMI (kg/m$^2$) | 29.35 ± 6.16 (n = 12) | 29.66 ± 6.76 (n = 10) |
| Back pain (VAS) | 7.73 ± 1.01 (n = 11) | 7.63 ± 1.06 (n = 8) |
| Leg pain (VAS) | 7.91 ± 1.14 (n = 11) | 7.63 ± 1.19 (n = 8) |
| BPI | 78.33 ± 10.22 (n = 12) | 80.89 ± 7.78 (n = 9) |
| EQ-5D | 11.67 ± 3.23 (n = 12) | 12.22 ± 3.11 (n = 9) |
| SLANSS | 17.00 ± 4.71 (n = 12) | 18.33 ± 3.84 (n = 9) |

Data are presented raw (n) for gender. All other data are presented as mean ± standard deviation (n). BMI = Body Mass Index; VAS = Visual Analogue Scale; BPI = Brief Pain Inventory; EQ-5D = EuroQol five-dimension questionnaire; SLANSS = Self-completed Leeds Assessment of Neuropathic Symptoms and Signs.

Table 3: MSNA frequency and MSNA incidence at baseline in the whole sample (n = 11), at baseline and follow-up in the final sample (n = 6) and summary of differences between baseline and follow-up in the final sample (n = 6).

| | | | **MSNA frequency (units/minute)** | **MSNS incidence (units/100 heart beats)** |
|---|---|---|---|---|
| Whole sample (n = 11) | Baseline | Mean ± SD | 4.10 ± 1.98 | 6.39 ± 3.39 |
| | | Median | 4.40 | 6.28 |
| | | Min | 0.80 | 0.96 |
| | | Max | 6.85 | 12.12 |
| Final sample (n = 6) | Baseline | Mean ± SD | 3.43 ± 1.34 | 5.13 ± 1.72 |
| | | Median | 3.40 | 5.40 |
| | | Min | 2.00 | 2.86 |
| | | Max | 5.20 | 7.42 |
| | Follow-up | Mean ± SD | 2.77 ± 1.56 | 4.19 ± 2.88 |
| | | Median | 2.10 | 2.86 |
| | | Min | 1.40 | 1.75 |
| | | Max | 5.20 | 8.97 |
| | Paired t-test/ Wilcoxon signed-rank test | Mean difference | 0.67 | 0.95 |
| | | 95% CI | -1.55, 2.89 | -1.94, 3.83 |
| | | p-value | > 0.05 | > 0.05 |
| | | Effect size | r = 0.315 | r = 0.344 |

Table 4: Time-domain HRV measures at baseline in the whole sample (n = 14), at baseline and follow-up in the final sample (n = 10) and summary of differences between baseline and follow-up in the final sample (n = 10).

| | | | **Mean RR (ms)** | **SDRR (ms)** | **Δ RR (ms)** | **RMSSD (ms)** | **pRR50 (%)** |
|---|---|---|---|---|---|---|---|
| Whole sample (n = 14) | Baseline | Mean ± SD | 912.52 ± 167.10 | 43.00 ± 20.07 | 243.64 ± 126.81 | 25.70 ± 18.10 | 8.72 ± 13.50 |
| | | Median | 917.65 | 38.24 | 199.00 | 22.66 | 2.53 |
| | | Min | 616.30 | 17.89 | 97.00 | 4.09 | 0.00 |
| | | Max | 1268.00 | 77.81 | 536.00 | 65.56 | 44.44 |
| Final sample (n = 10) | Baseline | Mean ± SD | 907.53 ± 181.84 | 39.63 ± 20.08 | 239.30 ± 142.89 | 27.88 ± 20.71 | 10.92 ± 15.49 |
| | | Median | 904.25 | 33.76 | 192.50 | 22.66 | 3.57 |
| | | Min | 616.30 | 17.89 | 97.00 | 4.09 | 0.00 |
| | | Max | 1268.00 | 76.31 | 536.00 | 65.56 | 44.44 |
| | Follow-up | Mean ± SD | 860.83 ± 160.40 | 31.13 ± 13.34 | 193.00 ± 91.93 | 22.31 ± 11.86 | 4.76 ± 4.33 |
| | | Median | 913.15 | 35.09 | 197.50 | 25.76 | 4.25 |
| | | Min | 525.80 | 6.49 | 32 | 1.71 | 0.00 |
| | | Max | 1037.00 | 49.28 | 374 | 38.00 | 13.57 |
| | Paired t-test/ Wilcoxon signed-rank test | Mean difference | 46.70 | 8.50 | 30.44 | 5.57 | 6.16 |
| | | 95% CI | -26.77, 120.18 | -1.72, 18.71 | -38.38, 99.27 | -5.43, 16.57 | -2.50, 14.83 |
| | | p-value | > 0.05 | > 0.05 | > 0.05 | > 0.05 | > 0.05 |
| | | Effect size | r = 0.455 | r = 0.595 | d = 0.472 | r = 0.362 | r = -0.354 |

Table 5: Frequency-domain HRV measures at baseline in the whole sample (n = 14), at baseline and follow-up in the final sample (n = 10) and summary of differences between baseline and follow-up in the final sample (n = 10).

| | | | **Total power ($ms^2$)** | **LF power ($ms^2$)** | **HF power ($ms^2$)** | **nuLF** | **nuHF** | **LF/HF** |
|---|---|---|---|---|---|---|---|---|
| Whole sample (n = 14) | Baseline | Mean ± SD | 2052.31 ± 2516.30 | 573.64 ± 629.24 | 407.97 ± 557.19 | 62.91 ± 21.03 | 38.01 ± 20.55 | 3.04 ± 3.24 |
| | | Median | 868.75 | 283.05 | 192.10 | 58.43 | 42.03 | 1.39 |
| | | Min | 201.20 | 16.55 | 14.84 | 23.78 | 8.38 | 0.31 |
| | | Max | 9213.00 | 2250 | 1676.00 | 95.71 | 76.60 | 11.42 |
| Final sample (n = 10) | Baseline | Mean ± SD | 1563.85 ± 1651.09 | 597.45 ± 716.21 | 522.02 ± 628.92 | 55.82 ± 18.96 | 44.75 ± 19.02 | 1.91 ± 1.94 |
| | | Median | 868.75 | 254.25 | 322.70 | 54.84 | 45.53 | 1.21 |
| | | Min | 201.20 | 16.55 | 14.84 | 23.78 | 13.57 | 0.31 |
| | | Max | 4964.00 | 2250.00 | 1676.00 | 86.63 | 76.60 | 6.39 |
| | Follow-up | Mean ± SD | 1066.55 ± 957.63 | 372.35 ± 598.51 | 287.90 ± 232.76 | 52.76 ± 20.79 | 47.98 ± 20.59 | 1.53 ± 1.19 |
| | | Median | 1020.25 | 179.30 | 274.80 | 56.51 | 43.76 | 1.29 |
| | | Min | 41.17 | 5.94 | 1.51 | 23.83 | 20.44 | 0.31 |
| | | Max | 3316.00 | 2026.00 | 728.20 | 80.41 | 76.75 | 3.93 |
| | Paired t-test/ Wilcoxon signed-rank test | Mean difference | 497.30 | 225.10 | 234.12 | 3.05 | -3.23 | 0.38 |
| | | 95% CI | -263.67, 1258.26 | -47.18, 497.39 | -136.22, 604.46 | -10.55, 16.66 | -16.85, 10.40 | -1.04, 1.81 |
| | | p-value | > 0.05 | > 0.05 | > 0.05 | > 0.05 | > 0.05 | > 0.05 |
| | | Effect size | r = -0.371 | r = -0.500 | r = -0.306 | d = 0.161 | d = -0.169 | r = -0.210 |

Table 6: Up, down and mean BRS at baseline in the whole sample (n = 13), at baseline and follow-up in the final sample (n = 10) and summary of differences between baseline and follow-up in the final sample (n = 10).

| | | | **Up (ms/mmHg)** | **Down (ms/mmHg)** | **Mean (ms/mmHg)** |
|---|---|---|---|---|---|
| Whole sample (n = 13) | Baseline | Mean ± SD | 10.10 ± 6.48 | 10.39 ± 8.23 | 10.43 ± 7.05 |
| | | Median | 7.39 | 9.23 | 8.45 |
| | | Min | 2.87 | 0.00 | 2.63 |
| | | Max | 23.64 | 28.15 | 25.14 |
| Final sample (n = 10) | Baseline | Mean ± SD | 9.35 ± 6.26 | 10.25 ± 8.54 | 10.08 ± 7.01 |
| | | Median | 6.82 | 9.61 | 7.01 |
| | | Min | 2.87 | 0.00 | 2.63 |
| | | Max | 23.64 | 28.15 | 25.14 |
| | Follow-up | Mean ± SD | 8.64 ± 4.68 | 12.23 ± 7.47 | 10.26 ± 5.39 |
| | | Median | 10.78 | 12.85 | 12.47 |
| | | Min | 0.00 | 1.04 | 1.04 |
| | | Max | 13.60 | 23.66 | 17.75 |
| | Paired t-test/ Wilcoxon signed-rank test | Mean difference | 0.71 | -1.98 | -0.18 |
| | | 95% CI | -3.94, 5.37 | -8.56, 4.60 | -4.27, 3.91 |
| | | p-value | > 0.05 | > 0.05 | > 0.05 |
| | | Effect size | r = -0.081 | r = -0.215 | r = -0.031 |

**FIGURE CAPTIONS**

Figure 1: Summary of study schedule. HR = heart rate; BP = blood pressure, MSNA = muscle sympathetic nerve activity; SCS = spinal cord stimulation.

Figure 2: Summary of participant progression through the study. HR = heart rate; BP = blood pressure, MSNA = muscle sympathetic nerve activity; SCS = spinal cord stimulation.

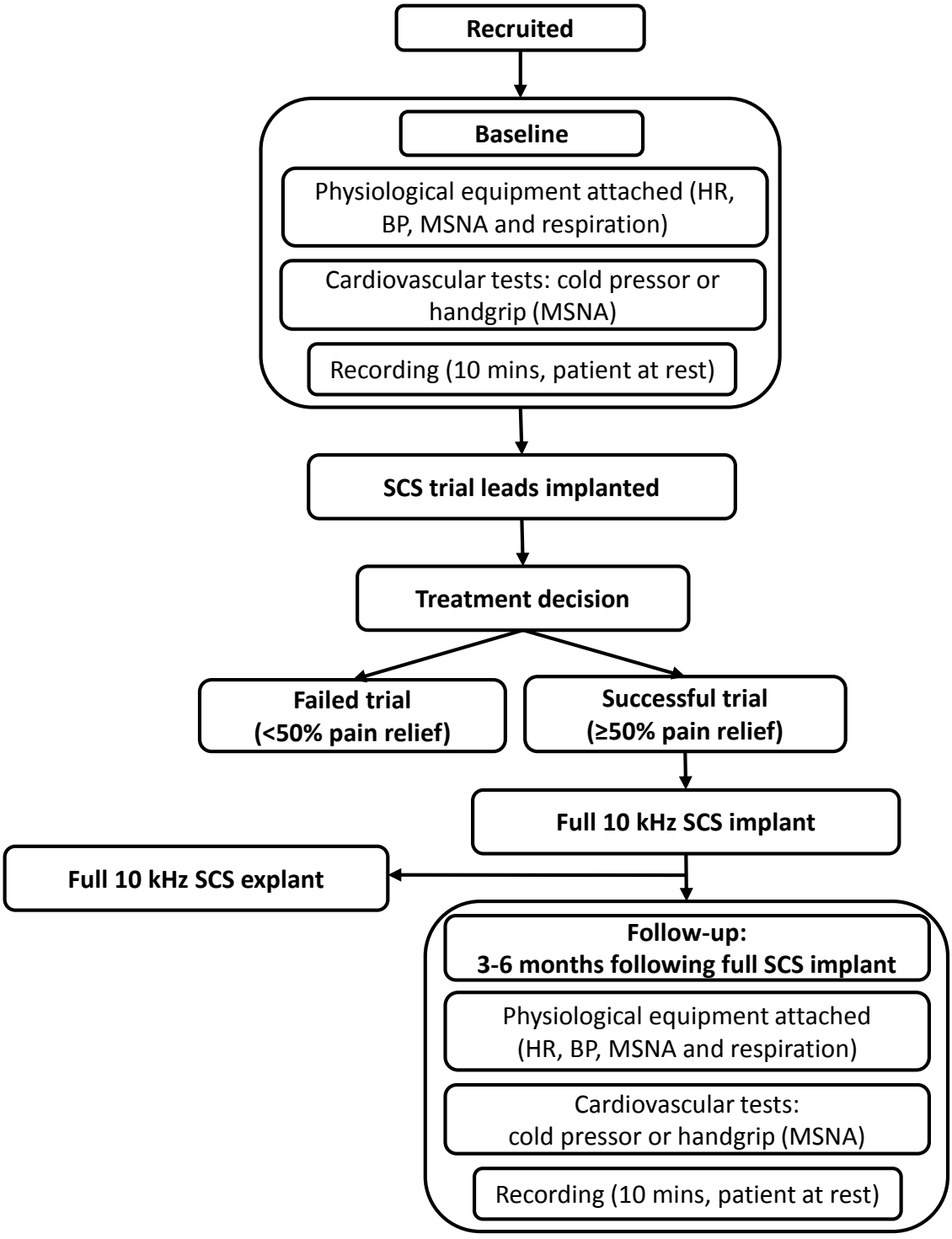
Figure 3: Example cold pressor test trace (a) from which individual action potentials were identified (b) and overlaid (c) to confirm a single MSNA unit.

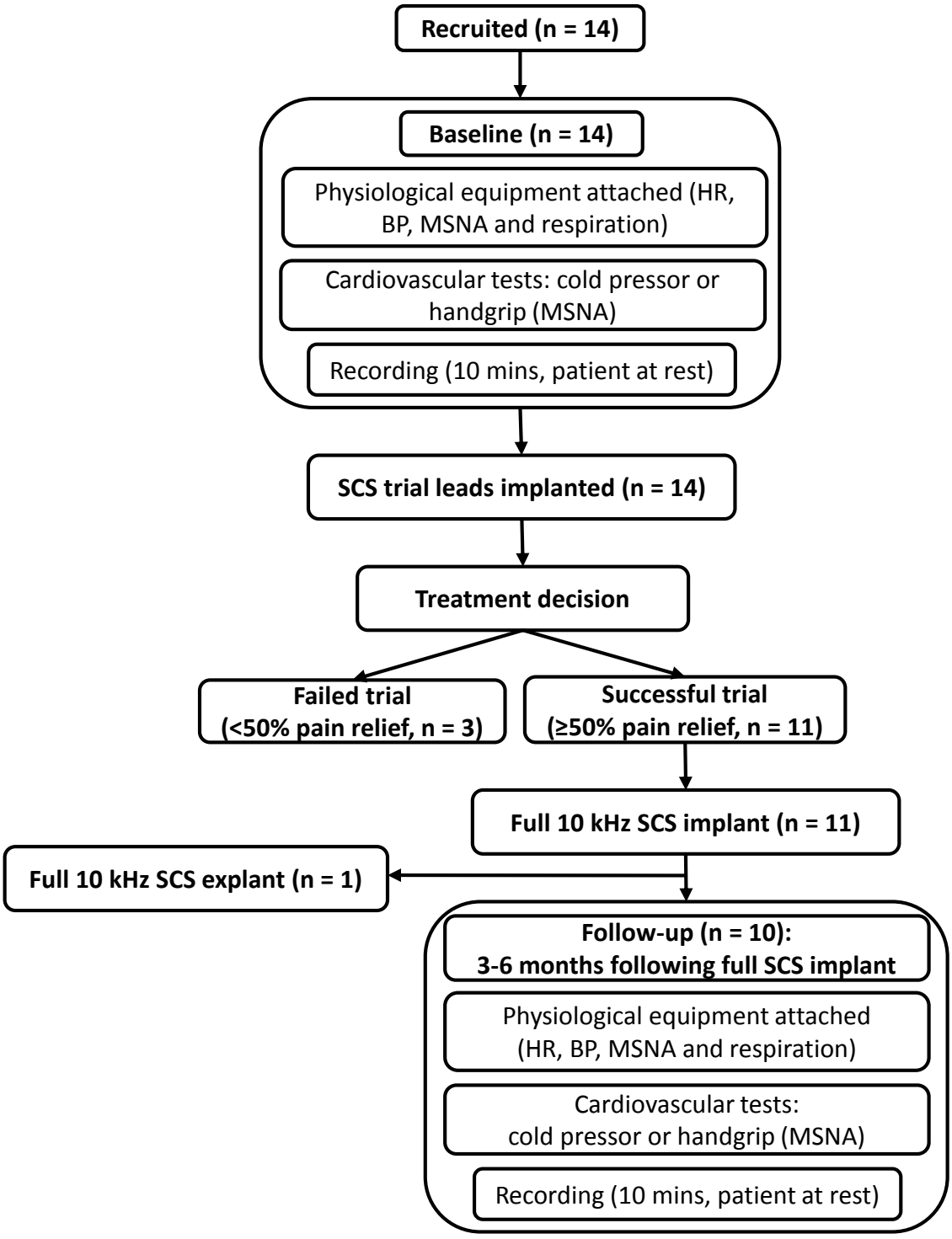
Figure 4: MSNA frequency (a) and MSNA incidence (b) for each participant during baseline and follow-up. Blue line indicates decreases between baseline and follow-up, yellow line indicates increases between baseline and follow-up, green line indicates no change, black line indicates the group mean and grey datapoints reflect participants who did not complete the follow-up visit.

Figure 5: Mean RR interval (a), SDRR (b), RMSSD (c), pRR50 (d) and Δ RR interval (e) for each participant in the final sample during baseline and follow-up. Blue line indicates decreases between baseline and follow-up, yellow line indicates increases between baseline and follow-up, green line indicates no change, black line indicates the group mean and grey datapoints reflect participants who did not complete the follow-up visit.

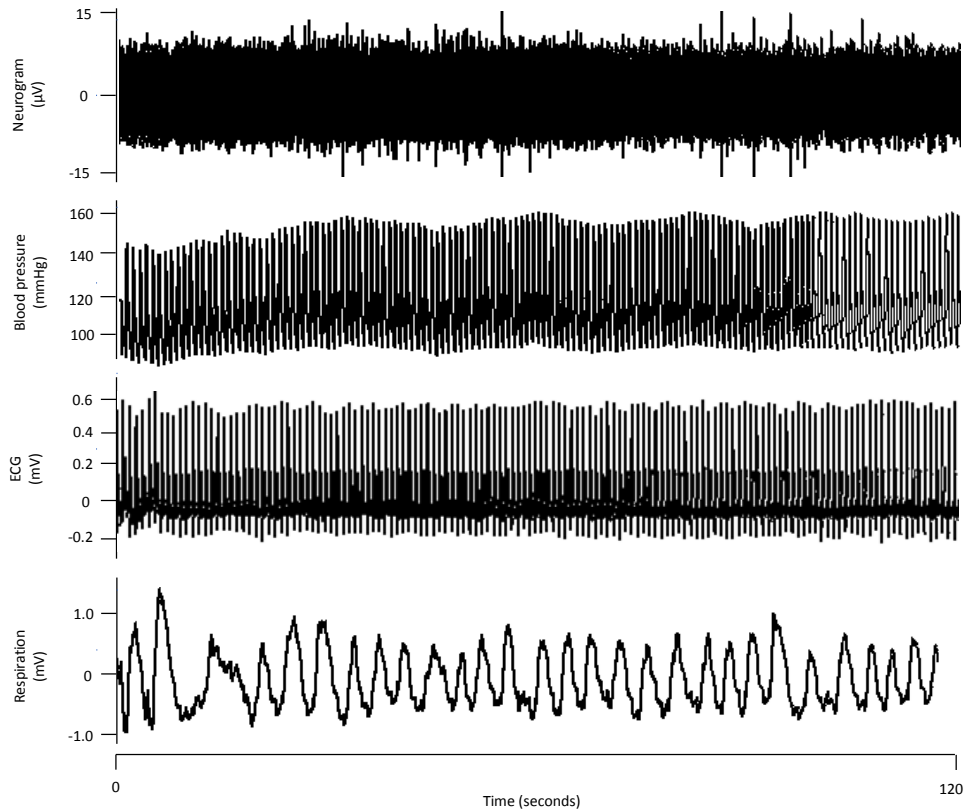
Figure 6: Total power (a), LF power (b), HF power (c), nuLF (d), nuHF (e) and LF/HF ratio (f) for each participant in the final sample during baseline and follow-up. Blue line indicates decreases between baseline and follow-up, yellow line indicates increases between baseline and follow-up, green line indicates no change, black line indicates the group mean and grey datapoints reflect participants who did not complete the follow-up visit.

Figure 7: Up BRS (a), down BRS (b) and mean BRS (c) for each participant in the final sample during baseline and follow-up. Blue line indicates decreases between baseline and follow-up, yellow line indicates increases between baseline and follow-up, black line indicates the group mean and grey datapoints reflect participants who did not complete the follow-up visit.

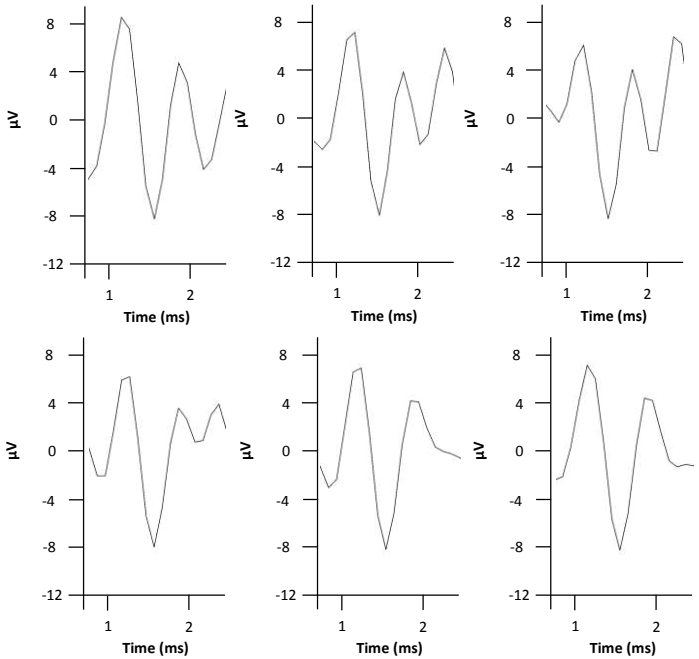

Recruited
Baseline
Physiological equipment attached (HR, BP, MSNA and respiration)
Cardiovascular tests: cold pressor or handgrip (MSNA)
Recording (10 mins, patient at rest)
SCS trial leads implanted
Treatment decision
Failed trial (<50% pain relief)
Successful trial (≥50% pain relief)
Full 10 kHz SCS implant
Full 10 kHz SCS explant
Follow-up: 3-6 months following full SCS implant
Physiological equipment attached (HR, BP, MSNA and respiration)
Cardiovascular tests: cold pressor or handgrip (MSNA)
Recording (10 mins, patient at rest)


Recruited (n = 14)
Baseline (n = 14)
Physiological equipment attached (HR, BP, MSNA and respiration)
Cardiovascular tests: cold pressor or handgrip (MSNA)
Recording (10 mins, patient at rest)
SCS trial leads implanted (n = 14)
Treatment decision
Failed trial (<50% pain relief, n = 3)
Successful trial (≥50% pain relief, n = 11)
Full 10 kHz SCS implant (n = 11)
Full 10 kHz SCS explant (n = 1)
Follow-up (n = 10): 3-6 months following full SCS implant
Physiological equipment attached (HR, BP, MSNA and respiration)
Cardiovascular tests: cold pressor or handgrip (MSNA)
Recording (10 mins, patient at rest)

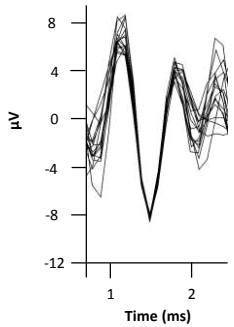
**a. Cold pressor test**



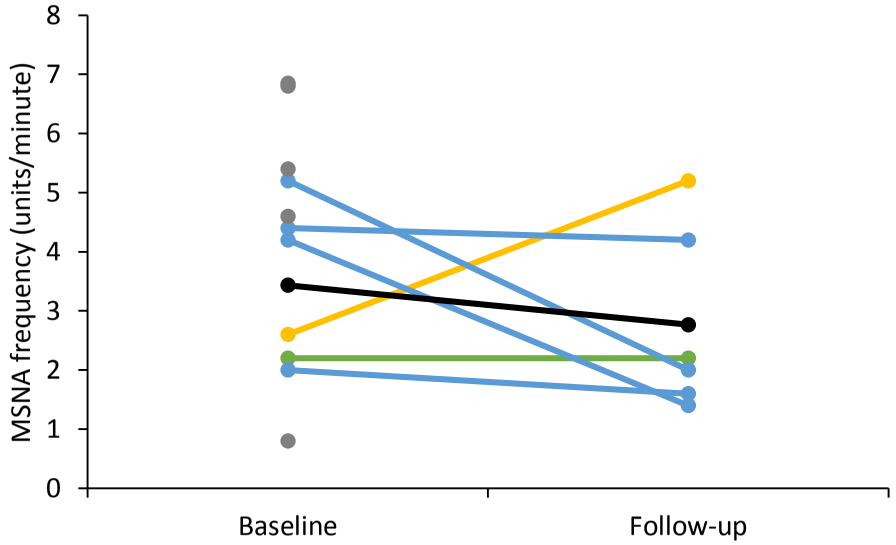

**b. Putative individual action potentials**



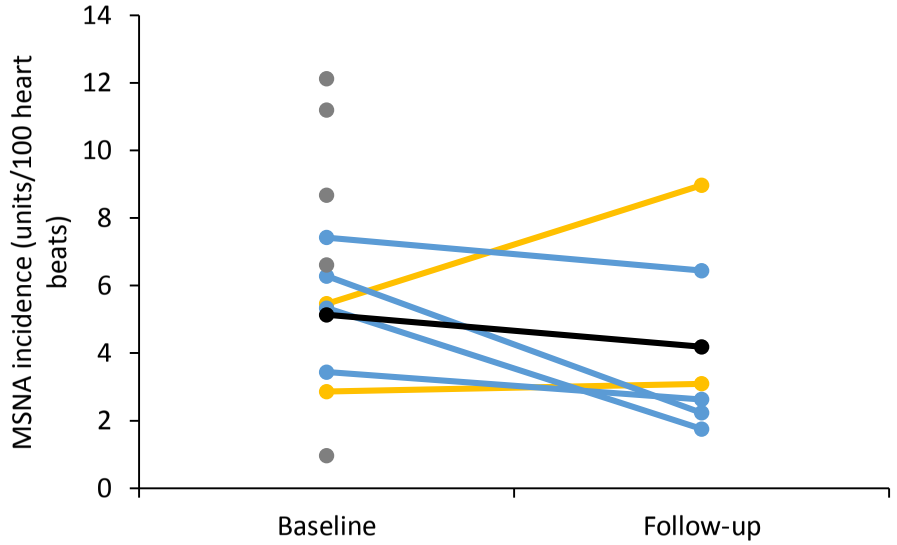

**c. Overlaid action potentials: confirmed MSNA unit**



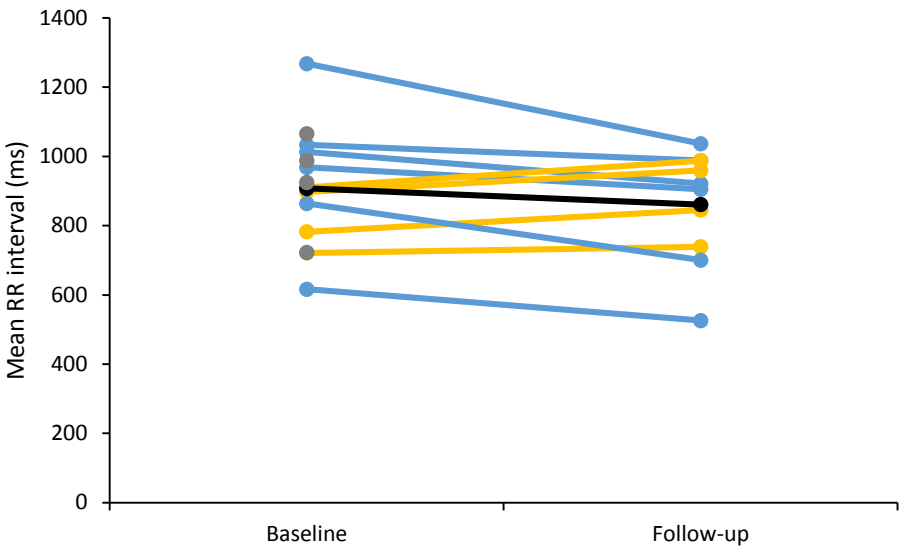
**a.**


MSNA frequency (units/minute)
0
1
2
3
4
5
6
7
8
Baseline
Follow-up

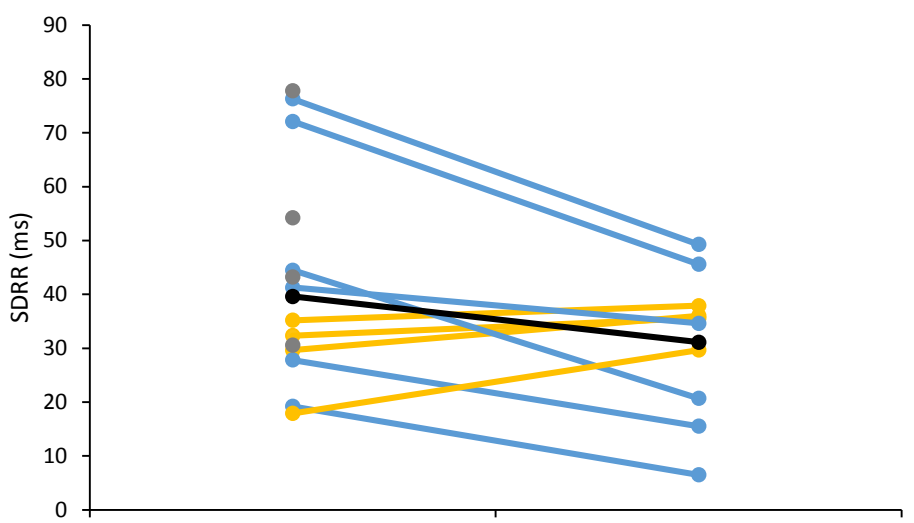
**b.**


MSNA incidence (units/100 heart beats)
0
2
4
6
8
10
12
14
Baseline
Follow-up

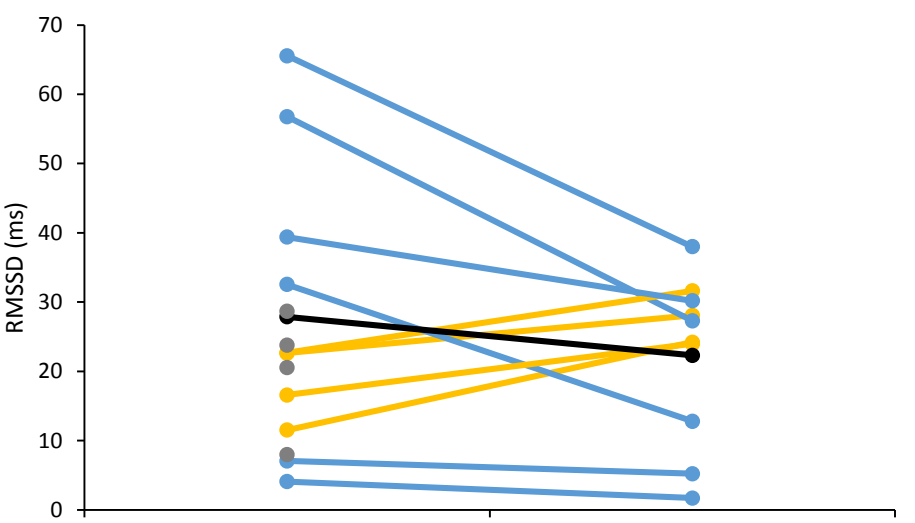
**a.**


1400
1200
1000
800
600
400
200
0
Mean RR interval (ms)
Baseline
Follow-up

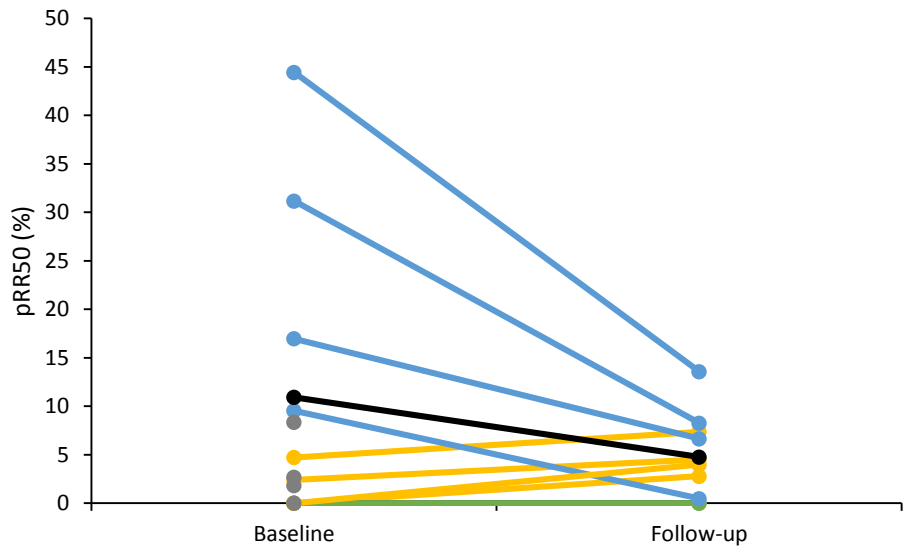
**b.**


90
80
70
60
50
40
30
20
10
0
SDRR (ms)
Baseline
Follow-up

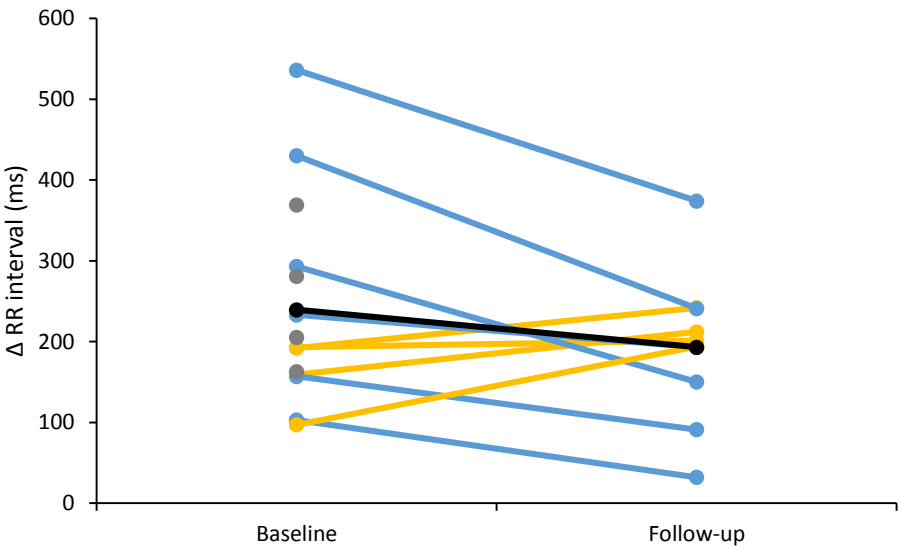
**c.**


70
60
50
40
30
20
10
0
RMSSD (ms)
Baseline
Follow-up

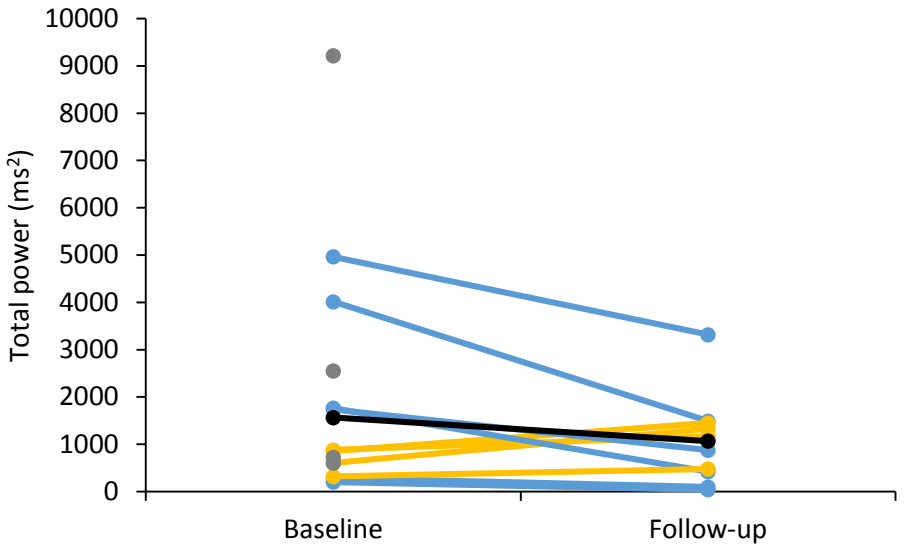
**d.**


50
45
40
35
30
25
20
15
10
5
0
pRR50 (%)
Baseline
Follow-up

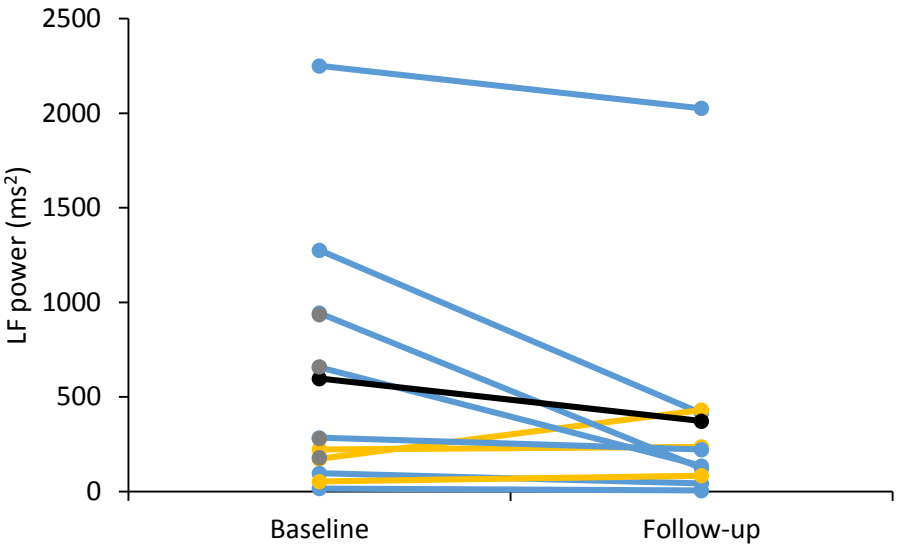
**e.**


600
500
400
300
200
100
0
Δ RR interval (ms)
Baseline
Follow-up

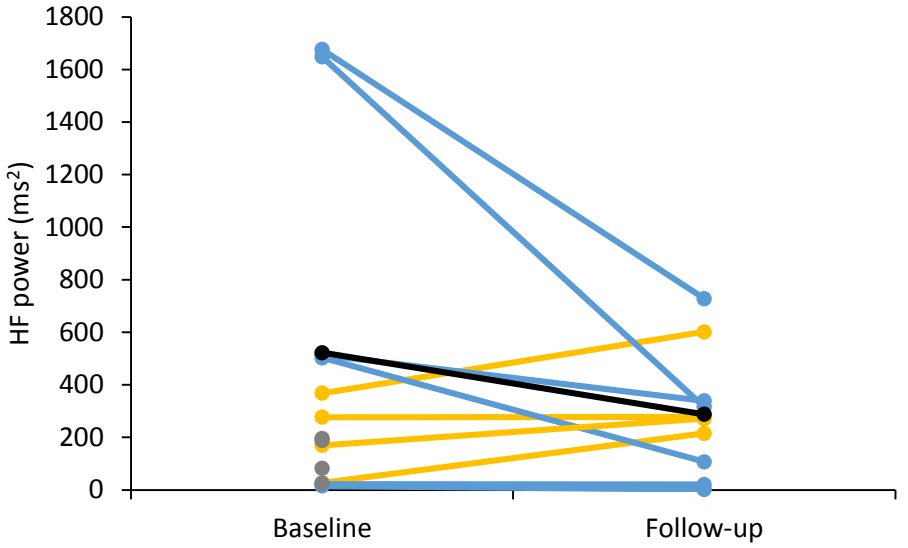
**a.**


Total power (ms²)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Baseline
Follow-up

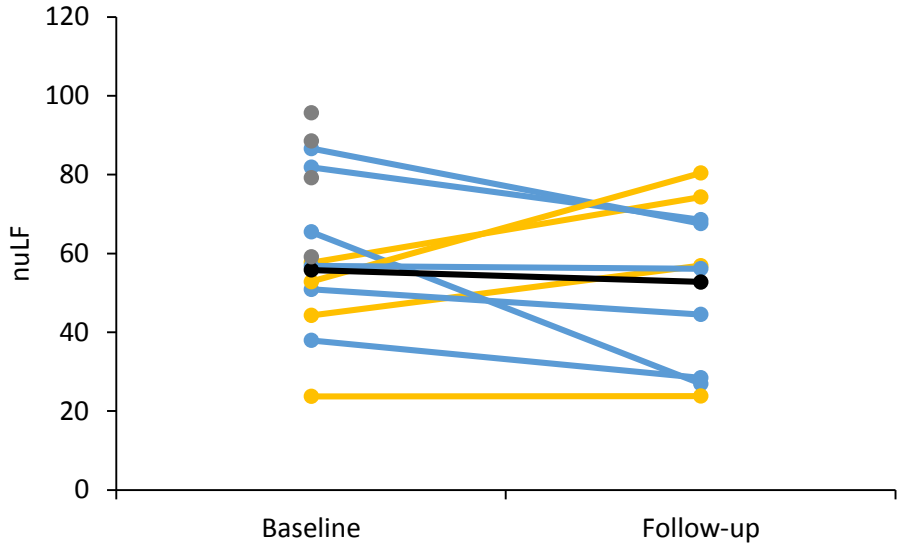
**b.**


LF power (ms²)
2500
2000
1500
1000
500
0
Baseline
Follow-up

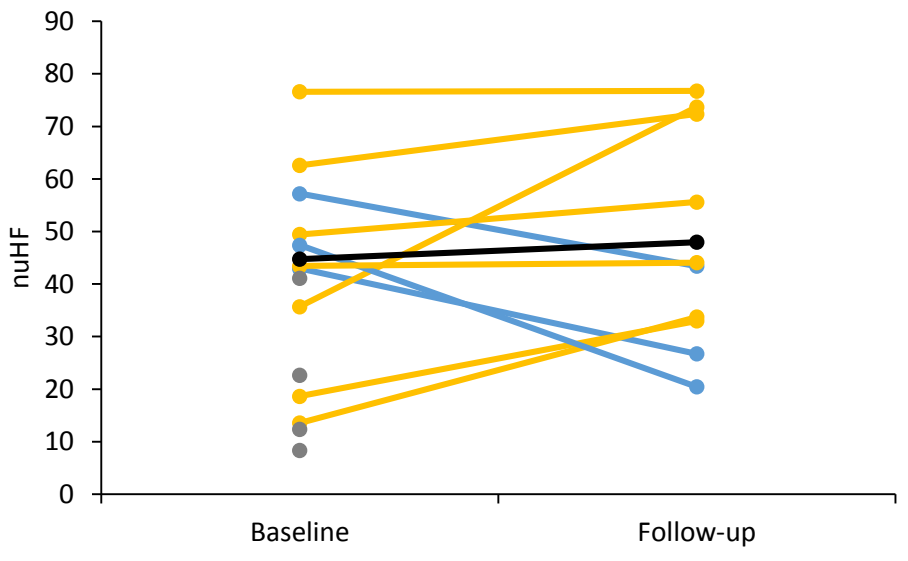
**c.**


HF power (ms²)
1800
1600
1400
1200
1000
800
600
400
200
0
Baseline
Follow-up

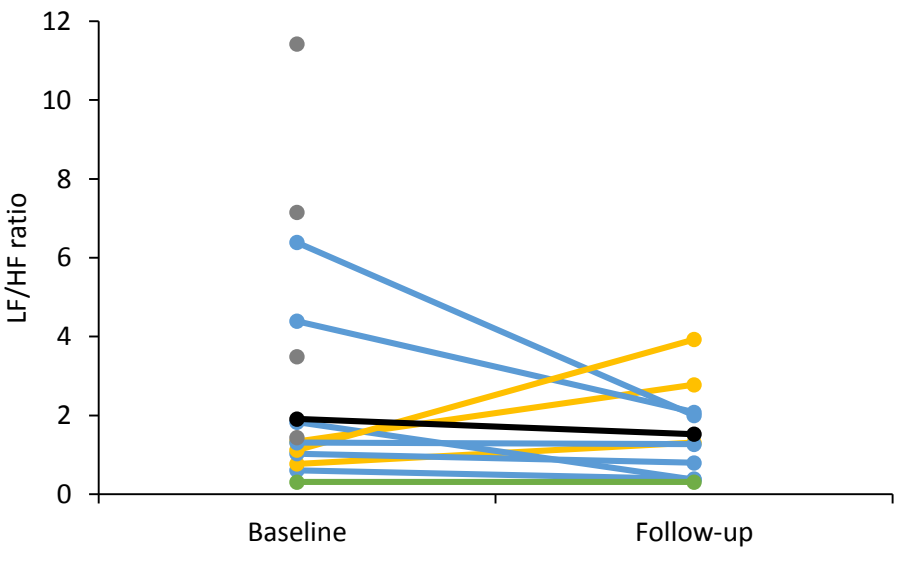
**d.**


nuLF
120
100
80
60
40
20
0
Baseline
Follow-up

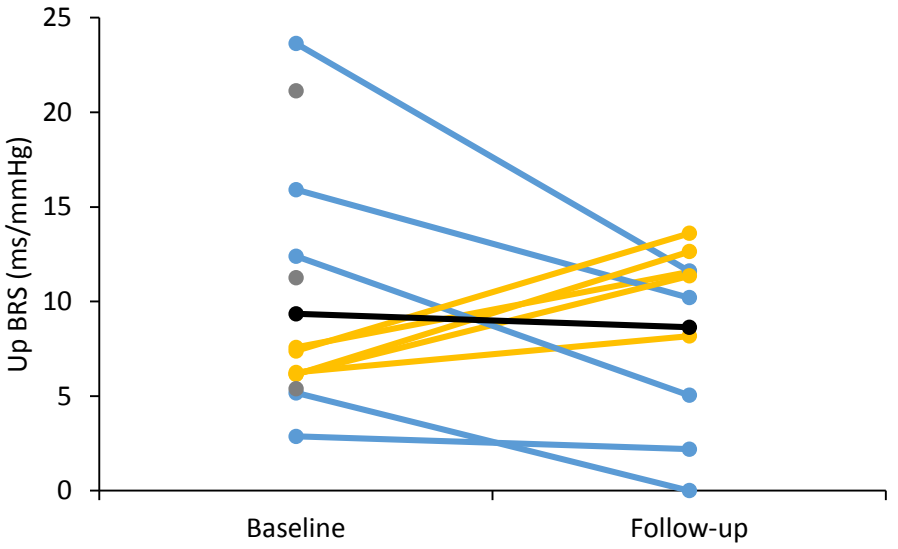
**e.**


nuHF
90
80
70
60
50
40
30
20
10
0
Baseline
Follow-up

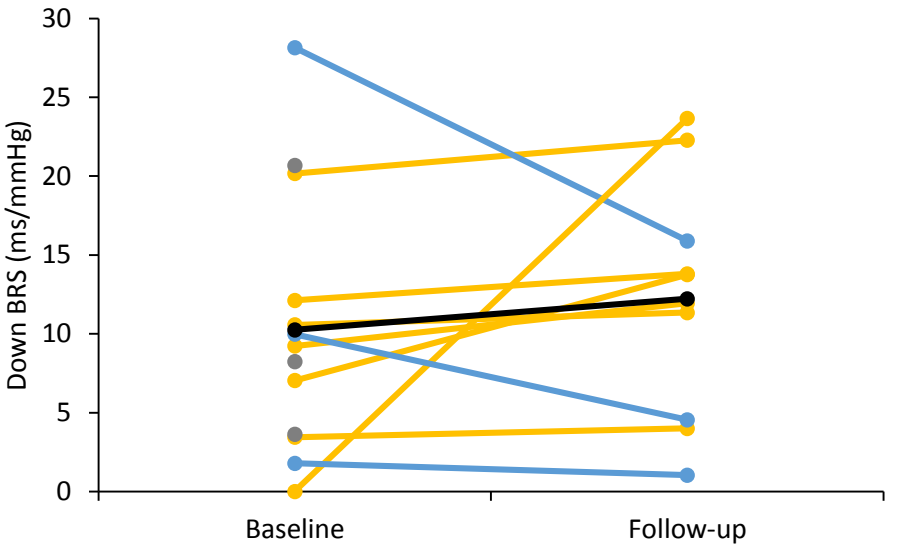
**f.**


LF/HF ratio
12
10
8
6
4
2
0
Baseline
Follow-up

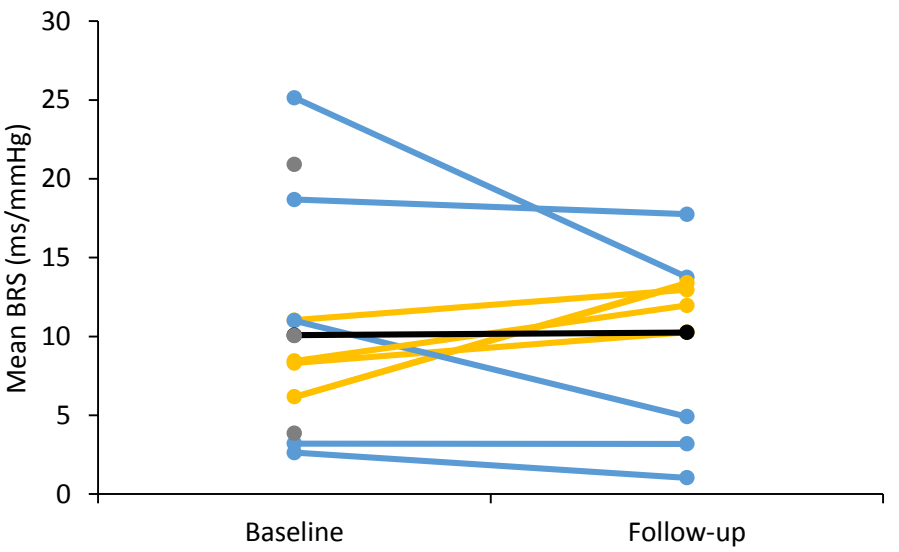
**a.**


Up BRS (ms/mmHg)
25
20
15
10
5
0
Baseline
Follow-up

**b.**


Down BRS (ms/mmHg)
30
25
20
15
10
5
0
Baseline
Follow-up

**c.**


Mean BRS (ms/mmHg)
30
25
20
15
10
5
0
Baseline
Follow-up