Pain-reactive Heart-Rate Variability in Sympathetically Disturbed and Non-Sympathetically Disturbed Individuals With Chronic Whiplash Associated Disorder (WAD)

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There is growing interest in the possible role of autonomic nervous system (ANS) dysfunction in whiplash associated disorders (WAD)[1, 2]. The role of the ANS in contributing to the onset or maintenance of other painful conditions, such as fibromyalgia syndrome (FM)[3-5] and complex regional pain syndrome (CRPS)[6], is well established. Schurmann and colleagues[6] evaluated sympathetic nervous system (SNS) functioning by monitoring changes in cutaneous blood flow in response to provocative stimuli including an inspiratory gasp (the sympathetic vasoconstriction response, or SVR) and demonstrated lost or diminished sympathetic reactivity in CRPS patients compared to controls. In WAD, ANS dysfunction may be related to whether patients recover of go on to chronicity. In a study by Sterling and colleagues, acute patients who go on to experience high levels of pain and disability 6-months later demonstrated a diminished SVR compared to controls[7]. In another prospective study of acute WAD patients, lack of SNS responsiveness within four weeks of the instigating motor vehicle accident (MVA), as measured by SVR, was predictive of pain and disability 6-months later[8]. In that study a number of potentially confounding factors were controlled, including initial pain and disability, age, range of movement, cold pain hypersensitivity, and self-reported symptoms of psychological trauma.

Another convenient method of evaluating ANS functioning is via heart-rate variability (HRV)[9]. Under normal conditions the R-R interval trace of cardiac activity demonstrates variability that is moderated by the parasympathetic nervous system (PNS). Decreased PNS activity or increased SNS activity will result in reduced HRV. High frequency (HF) activity (0.4 to 0.15 Hz), especially, has been linked to PNS activity. Activity in this range is associated with the respiratory sinus arrhythmia (RSA), a vagally-mediated moderation of heart-rate such that it increases during

inspiration and decreases during expiration. Less is know about the physiological inputs of the low frequency (LF) activity (0.04 to 0.15Hz), though recent consensus suggest it is influenced either by the SNS or a mixture of both the SNS and PNS [9]. Because both frequency components may be influenced by the PNS, SNS activity may be inferred by the ratio of LF to HF activity.

HRV is related to emotional arousal. HF activity has been found to increase under conditions of acute time pressure and emotional strain[10] and elevated state anxiety [11], presumably related to focussed attention and motor inhibition [11]. HRV has been shown to be reduced in individuals reporting a greater frequency and duration of daily worry [12]. In individuals with post-traumatic stress disorder (PTSD), HRV and its HF component is reduced compared to controls whilst the LF component is elevated. Furthermore, unlike controls, PTSD patients demonstrated no LF or HF reactivity to recalling a traumatic event.

HRV studies have also been used to examine autonomic function in the context of pain. FMS studies demonstrate reduced general ANS activity and markedly reduced nocturnal ANS activity[4], increased baseline SNS activity [5], and impaired SNS reactivity to stimuli including orthostatic and mental stress [5, 13]. To date, no studies of HRV have been conducted in WAD. For FMS, the combination of high basal SNS activity found in HRV studies and reduced SNS responsiveness found in HRV and blood-flow studies suggests that the SNS may be hyperactive but hyporeactive, which Martinez-Lavin and Hermosillo[14] suggest may be due to β-adrenergic receptor desensitization and down-regulation caused by chronic hyperstimulation.

The current study aims to investigate HRV in the daily life of patients with chronic WAD with high versus low SNS reactivity measured by SVR. It is anticipated that HRV will be reduced in those with SNS dysfunction. In addition, it is anticipated that

HRV reactivity to occasions of increased pain will differ between those demonstrating reduced SNS reactivity via SVR and those with normal SNS reactivity. Because HRV is associated with emotional arousal, HRV reactivity to occasions of elevated negative affect was also assessed.

Method

Participants

Participants consisted of 32 volunteers (5 males), aged 22 to 64 (M=40.8, SD= 10.1), reporting neck pain as a result of an MVC. Participants made telephone contact in response to advertisements in community newspapers. They were considered eligible if they met Quebec Task Force (QTF) (Spitzer et al., 1995) classifications of WAD grade II and lived within traveling distance of the University, and were excluded if they experienced concussion, loss of consciousness, or head injury as a result of the MVC, or reported a prior whiplash injury or a history of neck-complaints requiring treatment. Time since the MVC ranged from three to 64 months (M=27.15, SD=19.7). The majority of participants were either self-employed (n=15) or employed (n=14). Of these individuals, 59% were working usual hours, 31% were working reduced hours, and 10% were not working because of their injury. Two of the remaining participants reported doing home-duties and one was retired. Eighteen participants reported being involved in litigation, with three of those having had their claim settled.

All participants gave informed consent for their participation. They were remunerated for transport costs to the research unit. The study was approved by the University's Medical Research Ethics Committee.

Questionnaires

Injury-related and demographic details were recorded for descriptive purposes. Participants also completed a single 10cm VAS item indicating the average intensity of their neck pain, with anchors "No pain" and "Worst pain imaginable". They completed a booklet of eight questionnaires as part of an assessment battery used in previous studies[8].

Sympathetic Vasoconstriction Response

Skin blood-flow at the thenar eminence of both hands was measured using Laser Doppler flowmetry (Moorlab system, Moor Instruments, Devon, England). An inspiratory gasp was performed as a known means of provoking sympathetically mediated cutaneous vasoconstriction[6]. The extent of the vasoconstriction response was quantified via the quotient of intervals (QI), a measure of change in the blood-flow curve after provocation that takes into account the duration of perfusion decrease [6]. A median split was applied (QI= 50.77) to classify subjects into high (above median) and low (below median) SNS disturbance groups.

INSERT TABLE 1

Electronic Diary (ED)

Electronic diaries were used to measure momentary within-day reports of pain, positive affect, and negative affect, and trauma-symptoms during the prior hour. The ED required participants to respond to questions using a stylus-pen on the PDA's touch-sensitive screen. The ED contained 30 screens involving a range of questions about pain, emotional states, behavior and activities, medication and caffeine consumption, and pain coping and appraisals. Only those items related to the current

study are described and reported here. The pain and affect items employed a VAS-type format whereby participants selected a point on a 100-point line (recorded as a value between 0 and 1) using the PDA's stylus pen. The percentage-value of their rating was fed-back to participants. Also, at equal intervals along the rating scale verbal descriptors were provided to help participants anchor their responses (see Table 1). Participants were prevented from continuing to the next item until they had responded to the VAS scale. The trauma measures employed a check-list format whereby one, all, or any combination of options could be selected from a list of symptoms. Once they had completed an item participants were prevented from returning to previous items.

Pain intensity. Current neck pain was measured on a single VAS-type item, "The level of my neck pain at the present moment is:". Feedback anchors were based on Tursky, Jamner & Friedman's (1982; cited in Karoly & Jensen, 1987) 12-point verbal rating scale (see Table 1). The scale was measured zero to one.

Positive and Negative Affect. PA and NA were measured via six VAS-type items involving emotional adjectives proceeded by the question "To what extent do I feel this emotion right now:". The six adjectives were chosen based on the three items on the PA and NA scales of the Positive And Negative **** (PANAS) REF**** that demonstrated the highest corrected item-total correlations from a pilot dataset of 49 undergraduate students. The NA items "Nervous", "Distressed", and "Afraid" correlated r=0.52, 0.62, and 0.62 with the total NA scale , and the PA items "Enthusiastic", "Attentive" and "Inspired" correlated r=0.6, 0.6, and 0.67 with the total PA scale. Chronbach's alpha was 0.66 for the three-item PA scale and 0.8 for the three-item NA scale. The three-item PA and NA scales correlated r=0.92 and r=0.86 respectively with their full-item scales.

A principal components analyses of all diary entries (n=298) involving all six NA and PA item revealed two factors accounting for 48.4% and 45.1% of variance respectively. After Varimax rotation the NA items loaded 0.97 to 0.98 on the first factor, and the PA items loaded 0.93 to 0.97 on the other. Chronbach's alpha was 0.951 and 0.976 for the PA and NA scales respectively.

The three items in each scale were scored between zero and one and averaged to obtain a scale score.

Trauma symptomatology. The five items with highest item-total correlations from the Impact of Events Scale – Revised [16] Hyperarousal, Avoidance, and Intrusion scales were selected to measure those three constructs, based on data from a previous study of WAD patients [8]. Sleep-related items were not considered for inclusion because they would not be relevant for the majority of diary entries when sleep had not occurred during the previous hour. IES-R items eight, 11, 12, 17, and 22 were chosen from the Avoidance scale, one, three, six, nine, and 16 from the Intrusions scale, and four, 10, 18, 19 and 21 from the Hyperarousal scale. In the pilot dataset, scales based on those items correlated r=.85, r=.82, and r=.83 respectively with the total scales. On the ED, trauma-related symptoms were presented over three checklist-type diary screens with a total of fifteen options (see Table 1). On each screen participants were asked "With respect to the accident, which difficulties distressed or bothered me since the previous entry?". The number of endorsed items for each scale were averaged to obtain a total score between zero (no symptoms) and one (all symptoms).

Physiological Monitoring

ECG, respiration, and movement data was collected via the Lifeshirt system (Vivometrics Inc., Ventura, California). Participants wore a lycra vest that incorporates data cables, 2-axis accelerometers, and respiratory inductive

plethysmography (RIP) bands at the abdomen and rib-cage. Data was collected on a PDA worn in an over-the-shoulder satchel.

Heart-rate was collected via 3-lead ECG with two electrodes placed on the skin of the upper chest and one on the lateral surface of the abdomen. Respiratory rate (breaths per minute) was measured via RIP, incorporating measures of expansion and contraction at both the abdomen and rib-cage.

The Lifeshirt system includes accelerometers to measure movement over x-, and y-axes. A composite score combining both dimensions was used as a measure of motion for the current analyses. The manufactures suggest that readings of normal daily ambulation would vary between 2 and 5 for slow walking, 7 to 10 for medium-level walking, and 12 to 18 for faster paces.

Procedure

Participants attended the research centre, where they underwent a battery of physical and sensory tests used in prior studies [8] for approximately one hour, including the SVR assessment. They were fitted with the Lifeshirt system, and the process of fitting the system was demonstrated to them. Participants were guided through one entry of the electronic diary to familiarize them with the process and the diary items. Participants wore the Lifeshirt for at least one day, between 10:15am and 8:45pm, though they were encouraged to refit the Lifeshirt the following day for the same time-period. Preferably, their initial assessment was scheduled for approximately 8:00am and they wore the Lifeshirt home from that session, though when this was not possible they fitted the Lifeshirt themselves on the following day.

On the same days participants wore the Lifeshirt they were asked to complete the ED. EDs were programmed to ‘wake themselves up’ to emit alarms every hour between

11:00am and 8:00pm at a random time ±15 minutes either side of each hour. Alarms consisted of a "bell"-type alert that sounded continuously for one minute and then on the minute for the next nine minutes. After that time the diary put itself back to sleep until the next hour's alarm.

When an alarm was sounded the PDA opened a screen providing participants with options to *open*, *dismiss*, or *postpone* the diary entry. *Open* activated the electronic diary, *dismiss* cancelled the entry, and *postpone* allowed the subject to choose a period between 5 and 15 minutes to postpone the entry.

The diary emitted an alarm each minute if it was left unattended during an entry. It put itself to sleep, terminating the current entry, if it was left unattended for 4 minutes.

Data structure and analysis

If participants completed two days of monitoring their 'best' day was selected for analyses on the basis of which day had the most diary entries with corresponding HRV data.

Within Person Factor

Ratings of neck pain intensity from hourly electronic diary entries (beginning at 11:00 ± 15mins and ending at 20:30 ± 15mins) were used to specify high and low pain occasions for each participant. High pain occasions were defined as those diary entries where the pain rating was above the individual's mean pain rating, and low pain occasions where on which pain ratings fell below or were equal to the individual's mean pain rating. High and low NA occasions were specified in the same way.

Outcome Variables

Four indices of HRV were derived from participant's daily Lifeshirt monitoring: pNN50, HFnorm, LFnorm, and mNNm/b.

The R-R interval trace from the full day or monitoring was summarised into 5 minute blocks. pNN50, the number of adjacent R-R intervals within a 5 minute block differing by 50ms or more divided by the total number of adjacent R-R interval pairs was calculated for each five minute block as a general measure of HRV, as recommended by the HRV taskforce [9].

Spectral analysis was used to calculate total power (area under the curve) for each five minute block. The proportion of high (0.15 to 0.4Hz) and low (0.04 to 0.15Hz) frequency activity (HFnorm and LFnorm, respectively) were calculated as the ratio of HF or LF activity to total power minus very-low frequency activity. High HF activity is largely reflective of efferent vagal (parasympathetic) activity [9]. It has been proposed that LF activity is influenced by sympathetic activation [9] though this claim is more contentious.

As an alternate measure of the RSA, for each inspiratory/expiratory cycle the difference between the longest and shortest R-R intervals were calculated (NNmax/breath). These were averaged over the 5 minute blocks to provide mean NNmax/breath (mNNm/b).

For the purposes of within person analyses, the nearest five minute HRV windows ending prior to the onset of each diary entry were selected. HRV for low pain occasions was calculated as the mean value of 5-minute windows prior to low pain occasions, and visa versa of high pain occasions. Mean values of each outcome variable were also calculated for high and low NA occasions.

Results

Adherence

Two-hundred and ninety-eight diary entries were obtained with corresponding HRV data, giving an average of 9.31 entries per person (Max=10, Min=7).

On average, 4.65 (SD=1.49) diary entries per person were specified as low pain occasions and 4.65 (SD=1.38) as high pain occasions. Mean pain was significantly higher during occasions designated as high pain (M=.4568, SD=.2501) than during low pain (M=.2846, SD=.2368) occasions ($t(31)=-9.11$, $p<.0001$). For NA, an average of 5.24 (SD=1.57) diary entries were designated as low NA per person, and 4.17 (SD=1.69) as high NA. NA was rated as being significantly higher during high NA occasions (M=.2531, SD=.2582) than during low NA (M=.1563, SD=.2165) occasions ($t(28)=-7.08$, $p<.0001$). Three participants did not demonstrate any variation in their NA ratings (all=0), and were not included in analyses of high versus low NA occasions.

Analysis of Confounding Variables

To rule out possible confounding variables in the relationship between SVR group and HRV, *t*-tests were performed to ensure such variables did not vary systematically with SVR group status (see Table 2). Neither age, time since injury, VAS pain intensity, means of ED scales, nor means of Lifeshirt measures from all 5-minute windows prior to diary entries differed between high and low-QI groups.

INSERT TABLE 2

The potential confounding effect of other daily variables on pain intensity was evaluated by comparing high and low pain occasions on ED ratings of positive and negative affect, the ED checklist of trauma symptoms, and Lifeshirt data derived from all 5-minute windows prior to diary entries, including heart-rate, breaths-per-minute, and accelerometer activity (see Table 3). High and low pain occasions were associated with negative affect (with higher pain associated with higher NA), but no other potential confounds.

Four participants from the high-QI group and two from the low-QI group indicated on ED monitoring that they had consumed caffeine in the hour prior to at least one diary entry. For these six individuals HRV was compared for caffeine-hours versus non-caffeine hours in a series of paired-sample t-tests. HFnorm was marginally lower during caffeine hours (M=.26 vs .21, t(5)=2.56, p=.05), but there was no significant difference for LFnorm (t(5)=-2.29,p=ns), pNN50 (t(5)=1.42,p=ns) or mNNm/b (t(5)=1.42,p=ns). Caffeine was consumed during low-pain hours for the two participants in the low-QI group, and during high-pain hours for the four in the high-QI group. Because of the low frequency of caffeine consumption in the total sample no further steps were taken to control for caffeine consumption.

INSERT TABLE 3

HRV at high and low pain occasions

A series of two-way between (two levels: high-QI and low QI) and within-person (two levels: High pain and Low pain) ANOVAS were conducted to examine each of the four HRV measures.

For pNN50 main effects for group ($F(1,30)=.995$, p=ns) and pain ($F(1,30)=1.009$, p=ns) were not significant, but the interaction was ($F(1,30)=5.46$, $p=.026$). T-tests of simple effects revealed that HRV was greater in low pain than high pain occasions in the high-QI group only ($t(15)=2.65$, $p=.018$).

Normalised high-frequency R-R activity (HFnorm) was more prominent in the High than the low QI group ($F(1,30)=5.97$, $p=.021$). Neither a pain main effect ($F(1,30)=3.245$, p=ns) nor an interaction with pain status($F(1,30)=.018$, p=ns) was apparent.

INSERT FIGURES

The group($F(1,30)=2.16$, p=ns) and pain ($F(1,30)=.635$, p=ns) main effects and interaction ($F(1,30)<.001$, p=ns) were not significant for normalised low-frequency activity (LFnorm).

For mNNm/b there was a significant interaction ($F(1,30)=5.047$, $p=.032$). Simple effects investigated via t-tests revealed that the SVR groups differed in the low pain condition, with the high-QI group demonstrating higher RSA ($t(30)=-2.28$, $p=.03$). Neither the group ($F(1,30)=3.94$, p=ns) nor pain ($F(1,30)=.007$, p=ns) main effects were significant.

HRV at high and low NA occasions

The possible role of NA in accounting for the effects of pain on HRV were investigated by running the same analyses of pNN50, LFnorm, HFnorm, and mNNm/b for high and low NA occasions in high and low-QI groups. No main effect

for NA was found, nor were any interactions significant (see Table 4 for all tests statistics).

INSERT TABLE 4

Discussion

The current study was concerned with the autonomic nervous system functioning of individuals with a chronic whiplash-associated disorder. Sympathetic nervous system disturbance is a noted feature of persistent pain conditions such as fibromyalgia and CRPS, and ANS disturbance in WAD patients has also been proposed as a possible factor contributing to ongoing pain and disability [8]. Those with SNS disturbance demonstrated more high-frequency R-R interval activity. This type of HRV is associated with the respiratory sinus arrhythmia and has been linked to vagally mediated parasympathetic activity. Also, in this group occasions of high pain were associated with reduced HRV (as measured by pNN50). This may reflect a general reduction in autonomic activity in the context of pain, or increased sympathetic activity. Occasions of high pain were systematically associated with higher negative affect, and given that the literature demonstrates negative emotional states are associated with HRV[10-12], negative affect represented a possible alternative explanation for HRV reactivity to pain. However, analyses of NA-reactive HRV changes did not reveal any significant main effects of occasion or interactions with SVR group.

Changes in HRV associated with pain were not apparent in the normal SNS function group.

The SNS disturbed and non-SNS disturbed groups differed in baseline parasympathetic activity as measured by average RSA, with the SNS disturbed individuals demonstrating greater RSA when not in pain. During pain the groups did not demonstrate a difference.

Table 1: ED Scales, items, and feedback anchors terms

Scale	Question and feedback
Pain	A single VAS item: "*The level of my neck pain at the present moment is:*" Feedback anchors: *Not noticeable; Just noticeable; Very weak; Weak; Mild; Moderate; Strong; Intense; Very strong; Severe; Very intense; Excruciating*
Positive Affect	An average of three VAS-type items: *To what extent do I feel this emotion right now: ATTENTIVE* Feedback anchors: *Very slightly or not at all; A little; Moderately; Quite a bit; Very much* *To what extent do I feel this emotion right now: INSPIRED* Feedback anchors: *As above* *To what extent do I feel this emotion right now: ENTHUSIASTIC* Feedback anchors: *As above*
Negative Affect	An average of three VAS-type items: *To what extent do I feel this emotion right now: DISTRESSED* Feedback anchors: *As above* *To what extent do I feel this emotion right now: NERVOUS* Feedback anchors: *As above* *To what extent do I feel this emotion right now: AFRAID* Feedback anchors: *As above*
Trauma Symptoms	Three checklist-type screens, each with the question: "*With respect to the accident, which difficulties distressed or bothered me since the previous entry?*"
Intrusion	Checklist options: *Other things making me think about it; I thought about it without meaning to; Pictures about it popped into my mind; I had waves of strong feelings about it; Reminders brought back feelings of it*
Hyper-arousal	Checklist options: *I was jumpy and easily startled; I had trouble concentrating; I felt watchful or on-guard; Reminders led to sweating, nausea, racing heart, trouble breathing, or another physical reaction; I felt irritable and angry*
Avoidance	Checklist options: *I tried not to talk about it; I tried to remove it from my memory; I tried not to think about it; I didn't deal with my feelings about it; I stayed away from reminders of it*

Table 2. Characteristics of Sympathetic Vasoconstriction Response Groups: M (SD)

	Low-QI	High-QI	t-test (df=30)
Age	42.66 (10.28)	39.93 (9.89)	1.042, p=ns
Months since injury	26.06 (18.13)	28.25 (21.67)	-0.31, p=ns
VAS pain intensity	4.66 (2.41)	5.01 (2.26)	-0.431, p=ns
Mean of ED ratings			
Pain	0.37 (0.24)	0.38 (0.23)	-0.119, p=ns
Positive Affect	0.28 (0.25)	0.36 (0.26)	-0.86, p=ns
Negative Affect	0.18 (0.25)	0.19 (0.24)	-0.198, p=ns
Trauma Symptoms	0.16 (0.16)	0.13 (0.17)	0.44, p=ns
Mean of physiological monitoring (all five-minute windows)			
Accelerometer Activity	1.89 (0.63)	2.2 (0.88)	-1.142, p=ns
Heart Rate	86.77 (11.89)	89.68 (12.31)	-0.68, p=ns
Breaths per minute	24.33 (4.61)	22.83 (3.62)	1.024, p=ns

Table 3. Comparison of High and Low Pain Occasions

	Low Pain	High Pain	
Positive Affect	0.33 (0.27)	0.32 (0.25)	0.928 (31), p=ns
Negative Affect	0.17 (0.23)	0.2 (0.26)	-2.809 (31), p=0.009
Trauma Symptoms	0.14 (0.17)	0.15 (0.17)	-1.213 (31), p=ns
Accelerometer Activity	2.16 (1.37)	2.02 (0.89)	0.586 (31), p=ns
Heart-rate	87.24 (11.64)	88.63 (13)	-0.942 (31), p=ns
Breaths per Minute	23.97 (4.68)	23.33 (4.34)	1.122 (31), p=ns

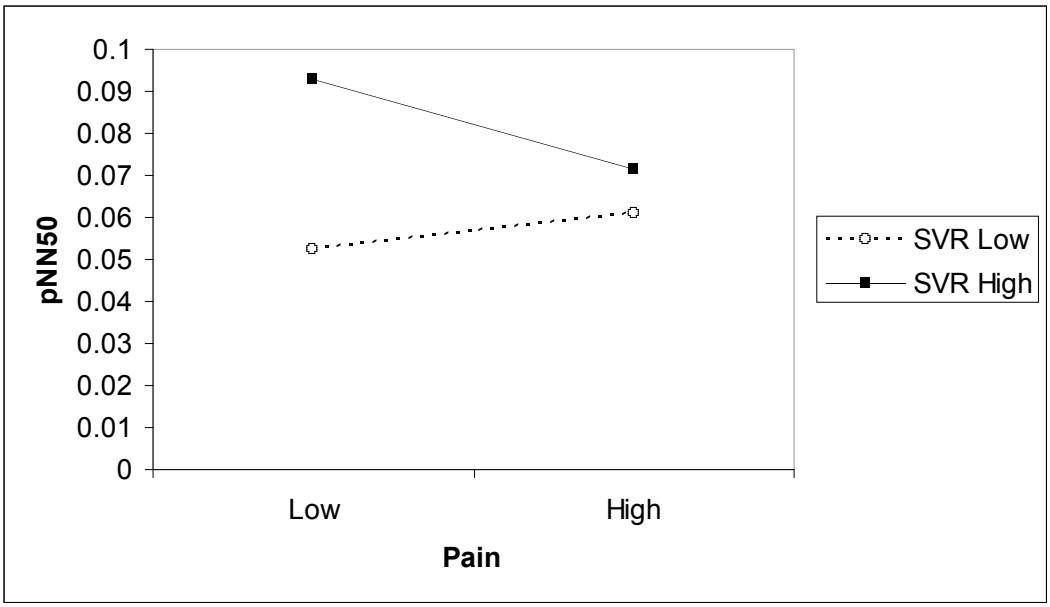

Figure 1. pNN50 in high and low-QI groups at high and low pain occasions

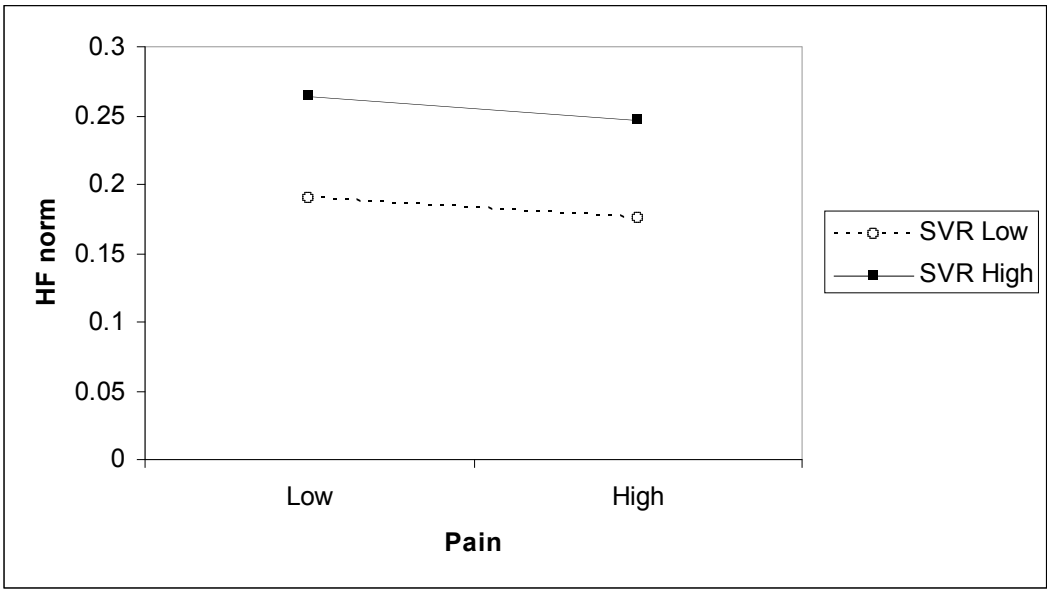

Figure 2. HFnorm in high and low-QI groups at high and low pain occasions

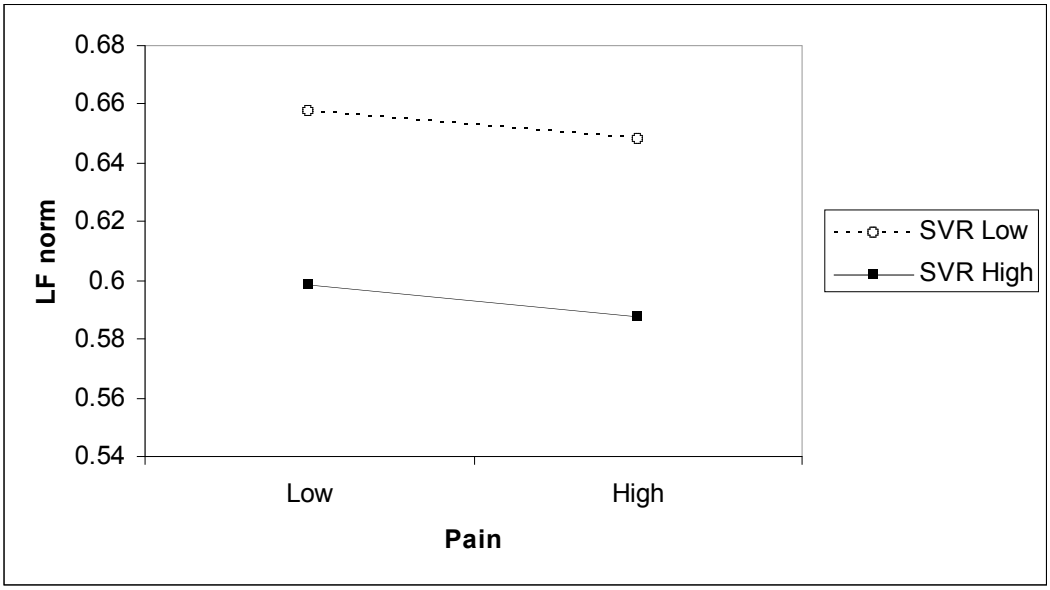

Figure 3. LFnorm in high and low-QI groups at high and low pain occasions

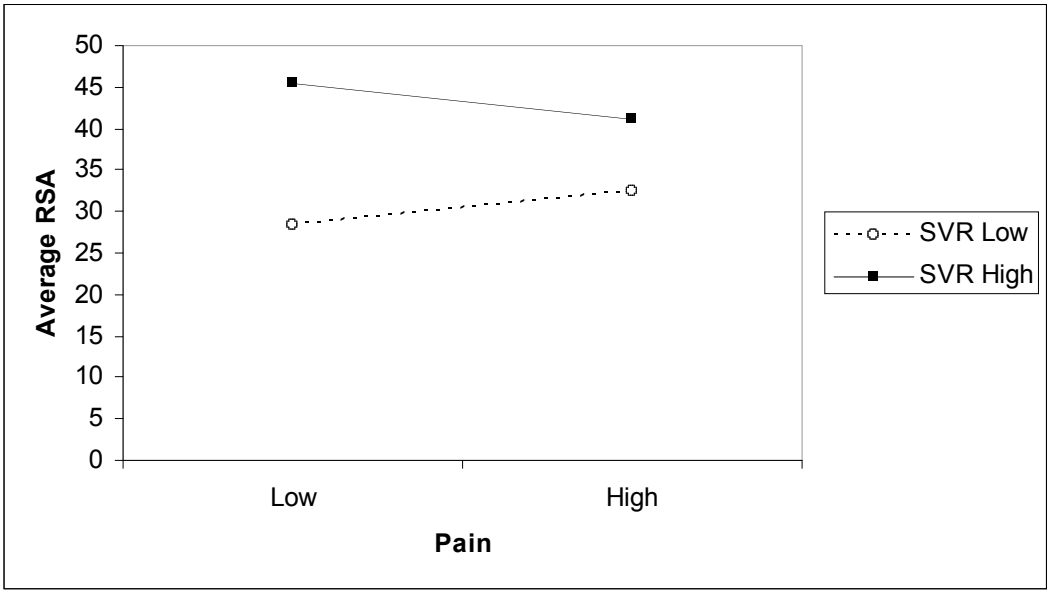

Figure 1. RSA in high and low-QI groups at high and low pain occasions

Table 4. Test statistics for F-tests of mean HRV in low vs high NA occasions (Within) for high and low-QI groups (Between)

Criterion	Within	Between	Interaction
pNN50	0.109	0.407	0.854
LFnorm	2.03	1.07	1.003
HFnorm	0.433	3.71	1.37
mNNm/b	0.894	3.14	0.023

In all cases df(1,27), p=ns

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