

## Cross-sectional Study



## Patients with Impaired Descending Nociceptive Inhibitory System Present Altered Cardiac Vagal Control at Rest

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**Background:** Patients with chronic musculoskeletal pain have a higher chance of presenting impairment in cardiovascular autonomic modulation, which may have implications for cardiovascular events. The autonomic nervous system plays an important role in pain modulation. However, it is unclear whether patients with inefficient descending nociceptive inhibition have poorer cardiovascular autonomic modulation.

**Objective:** To compare the cardiovascular autonomic modulation of patients with musculoskeletal pain who had normal versus impaired functioning of descending nociceptive inhibitory system (DNIS).

**Study Design:** A cross-sectional study.

**Setting:** Physiotherapy outpatient service.

**Methods:** Fifty-six patients with musculoskeletal pain were included. Conditioned pain modulation was assessed by the difference of algometric values held in the dorsal forearm and tibialis anterior muscle, before and after a thermal pain stimulus was employed via the cold pressure test (CPT). Patients with inefficient DNIS in both sites were classified as impaired responders ( $n = 14$ ). The others were classified as normal responders ( $n = 42$ ). Cardiac autonomic modulation was monitored at rest by heart rate variability (HRV). The blood pressure response to the CPT was used as a proxy of sympathetic responsiveness.

**Results:** Most of the patients were women (60%) and had chronic pain (75%). The groups had similar demographic characteristics. Patients with impaired DNIS showed lower HRV [RMSSD ( $P = 0.020$ ), SDRR ( $P = 0.009$ ), HF ( $ms^2$ ) ( $P = 0.027$ ), LF ( $ms^2$ ) ( $P = 0.004$ ), and total power ( $P = 0.002$ )]. The blood pressure response to CPT was similar between groups (systolic pressure,  $P = 0.813$ ; diastolic pressure,  $P = 0.709$ ).

**Limitation:** Physical activity level, emotional changes, and visceral pathologies can alter the autonomic nervous system and may represent potential confounders. The low number of patients may have biased the results.

**Conclusion:** Patients with impaired DNIS presented lower resting HRV, indicating an altered vagal control of the heart. In contrast, the blood pressure response to a sympathoexcitatory stimulus was preserved.

The study was approved by the Research Ethics Committee of Augusto Motta University Centre (CAAE number: 46245215.9.0000.5235), and all patients signed the Informed Consent Form.

**Key words:** Musculoskeletal pain, autonomic nervous system, heart rate, chronic pain, diffuse noxious inhibitory control, blood pressure, sympathetic nervous system, parasympathetic nervous system

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**P**ain has become a public health problem since its cost is higher than cardiovascular diseases, cancer, and diabetes (1). Many patients seeking treatment for pain have its origin in the musculoskeletal system, which affects about 1.7 billion people in the world (2). Thus, understanding the mechanisms of musculoskeletal pain is vital to offer proper treatment (3). Pain processing depends on the interaction of multiple neurobiological processes across the central and peripheral nervous systems (4). Also, the function of the descending nociceptive inhibitory system (DNIS) has a critical role in patients with musculoskeletal pain (5).

The impairment in DNIS is notably observed in patients with pain in remote areas from the initial injury (i.e., widespread pain). Widespread hyperalgesia is associated with less effective endogenous pain modulation (6). Impaired DNIS has been reported in many clinical conditions (5), including acute and chronic pain states (7). The inefficiency of the DNIS may contribute to the development and maintenance of central sensitization (5). Nonetheless, widespread hyperalgesia and central sensitization phenotypes are not present in every patient with chronic pain (6,8). Thus, the identification of subgroups of patients with pain is crucial for pain management and those with musculoskeletal pain with impaired DNIS may represent a potential subgroup for a tailored mechanism-based treatment.

The causes of DNIS impairment are still under debate, but alterations in the autonomic nervous system may play a role, due to anatomical, experimental, and clinical evidence. The anatomic reason is that several areas in the central nervous system involved in DNIS overlap with areas that directly influence brainstem autonomic neurons (i.e., anterior cingulate cortex, insular cortex, and amygdala) (9). Experimental evidence has consistently shown that a sustained pain stimulus alters both pain processing and autonomic regulation (10). In addition, patients with chronic musculoskeletal pain have a higher chance of presenting cardiovascular events (11). Indeed, patients classified with chronic pain, using a broad definition, demonstrated lower resting heart rate variability (HRV) and higher prevalence of hypertension diagnosis compared to pain-free controls (12). Noteworthy, however, the presence of altered cardiovascular autonomic modulation, especially in patients with the DNIS inefficiency, has not been demonstrated. And, if confirmed, the impairment in cardiovascular autonomic modulation could have relevant clinical value, since it would depict a subgroup

of patients with pain, with a higher chance to develop cardiovascular events (13,14).

This study aimed to compare the cardiovascular autonomic modulation among patients with musculoskeletal pain, with and without efficient DNIS. The efficiency of the DNIS was assessed via the conditioned pain paradigm with the cold pressor test (CPT), which is the most common method used for conditioned pain modulation (CPM) assessment (15). The cardiovascular autonomic modulation was assessed via 1) the analysis of the resting HRV, which provides indices of parasympathetic control of heart rate, and 2) blood pressure (BP) response to the CPT, which is a proxy of the sympathetic responsiveness to the stressor stimulus. Accordingly, we hypothesised that patients with inefficiency of the DNIS could have lower resting HRV and higher BP increase in response to the CPT than those counterparts who pursue efficient DNIS.

## **METHODS**

### **Study Design**

This study has a cross-sectional design, and it is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) requirements (16).

### **Study Patients**

Patients with musculoskeletal pain of the outpatient physiotherapy of Gaffrée and Guinle University Hospital, were enrolled when they sought treatment between November 2015 and May 2016. The study included patients who met simultaneously the following criteria: have musculoskeletal pain in some body segment and age above 18 years, regardless of gender and the clinical diagnosis. Musculoskeletal pain is defined as pain perceived in a region of the body with muscular, ligament, bone, or joint origin (17). The study excluded patients who had a surgical procedure in the spine, pregnant women, patients with rheumatologic diagnosis in the acute inflammatory phase, tumors, pacemaker carrier, cardiac arrhythmia or transplanted heart, cardiovascular medicine use, have ingested foods and drinks containing caffeine on the day of the experiment, had consumed alcoholic drinks in the last 24 hours, being illiterate or could not complete the self-reported questionnaires.

The study was approved by the Research Ethics Committee of Augusto Motta University Centre (CAAE number: 46245215.9.0000.5235), in accordance with

the Helsinki Declaration of 1975. All patients who met the eligibility criteria signed the informed consent form prior to the study procedures.

### Procedures

Patients were referred for initial evaluation consisting of the clinical history and physical examination. The acquisition of sociodemographic and clinical information was performed by an instrument containing demographic data (full name, gender, age, address, educational level, occupational, marital status) and characteristics of musculoskeletal pain (pain location, pain intensity, pain duration) and physical exercise behaviour.

Pain intensity was measured using the Numeric Pain Rating Scale (NPRS) from 0 to 10 where 0 is no pain and 10 is the worst pain possible. The duration of pain was recorded in months and patients were classified with chronic musculoskeletal pain if they had pain for more than 3 months according to the International Association for the Study of Pain definition. The physical exercise behaviour was self-reported and it was defined as a form of physical activity that is planned, structured, repetitive, and aims to improve or maintain physical fitness (18). The completion of the questionnaires was supervised by an examiner (E1) for clarification in case of uncertainties.

After completing the survey, patients were referred for evaluation of cardiac autonomic modulation. First, the patients underwent the cardiac autonomic modulation monitoring at rest by HRV, as a proxy of the vagal control of the heart. Then, the CPT was conducted and the BP response was measured, which was considered a proxy of the sympathetic activation. The CPM evaluation was conducted after the CPT. The evaluation of cardiac autonomic modulation was carried out by an examiner (E1), while the CPM evaluation was obtained by another examiner (E2).

### Measuring Instruments

HRV was recorded as beat-by-beat intervals (RR interval) sampling at a rate of 1000 Hz (Polar RS800cx; Polar, Finland). Patients were initially instructed to rest in the supine position for 10 minutes. After this initial period, the HRV was recorded by a 10-minute period in the same position. The RR interval was transferred to a computer by an interface with an infrared device for signal emission (Polar, Finland) and recorded in the software Polar ProTrainer 5 - Version 5.40.170 (Polar, Finland). Data were exported from Protrainer 5 software

in ascii format (.txt) and analyzed in Kubios software, version 2.2 (University of Eastern Finland). The HRV was analyzed in the time and frequency domain. The time domain analysis was performed by the standard deviation of the RR interval (SDRR) and the square root of the mean squared differences of successive RR intervals (RMSSD) measured in ms. RMSSD was used as an index of cardiac vagal modulation, since it is less affected by respiration, and thus, is a suitable outcome measure for outpatient studies (19). The frequency domain analysis was performed from the high-frequency (HF) component ranging between 0.15 and 0.4 Hz. The absolute and normalized power of the HF band of HRV was used as another indicator of cardiac vagal modulation.

The BP response to the CPT was used as a proxy of sympathetic responsiveness. The BP at rest was measured in the supine position using a mercury sphygmomanometer (RD 202 model, Unitec). Then, the patient was asked to immerse the nondominant hand in a container with cold water, with a temperature between 1°C and 4°C, monitored by a thermometer (5130 model, Incoterm), for up to 1 minute. The volunteer was instructed to remain with the hand immersed in water without making muscle contractions, changes in the segment, or decubitus. The withdrawal of the hand from water was allowed when the patient could no longer tolerate the painful stimulus. The BP measurement was performed with the inflation of the cuff after 40 seconds from the start of the test, or at the moment that the individual interrupted the test. Room temperature, humidity, lighting and noise were maintained constant during the entire procedure. The difference between the final and initial BP (Delta) was used as a measure of cardiac sympathetic activation and larger differences are due to increased sympathetic activation (20).

The CPM was measured by the conditioning stimulus of pain during the CPT. The CPM is an appropriate method to assess the diffuse noxious inhibitory control (21). The conditioning stimulus was the immersion of the hand and forearm in a bucket of ice water. The pressure pain threshold (PPT) was measured using a digital pressure algometer (model Force Ten FDX, Wagner Instruments, Greenwich, USA). Pressure algometry has been extensively used in healthy individuals and patients with different medical conditions (22-24), and it is recommended for clinical practice because of its low cost, high reliability (22,25), and good repeatability (26). Previous studies demonstrated adequate clinimetric properties to assess neck muscles (23,25),

first dorsal interosseous muscle of the hand (22), tibialis anterior muscle (25), and patients with myofascial pain (27). This test was performed before and after one minute of the CPT, and the thresholds were compared. Tibialis anterior muscle and the distal part of the dorsal forearm, which had not been immersed in water, were chosen to be evaluated due to the lack of relation with patients' musculoskeletal complaints. The operation of the pressure algometer and measurement of PPT were explained to patients prior the assessment. In addition, a familiarization procedure was carried out with the pressure algometer by applying pressure to the dominant forearm to ensure that the test had been understood. The force was gradually increased (rate of 1 kilograms-force/s) until the feeling of pressure from the initial subject was changed to pain. The PPT was recorded in kilograms-force (Kgf) when the patient gave the verbal command of pain.

Classification of the efficiency of the DNIS. There were 2 strategies used to refine the identification of the efficiency of the DNIS because of the absence of the uniform protocols for conducting CPM (28) and the lack of standards for the calculation of DNIS (29): (1) the evidence of impaired DNIS in 2 sites; (2) the error of the measurement using a digital pressure algometer. Then, only patients with the inefficiency of the DNIS in both locations (the tibialis anterior muscle and the distal part of the dorsal forearm) were classified as impaired responders while the other patients were classified as normal responders. An upper and a lower limb sites were used to avoid the inclusion of the patients with peripheral sensitization according to recent recommendations for CPM (28). Also, the efficiency of the DNIS was assessed by calculating the difference between the PPT values in CPT (final value – initial value). Negative values represented an inefficiency of the DNIS, and positive values were considered a normal response of the DNIS. We considered the standard error of measurement because it provides an estimation of the error associated with the measurement expressed in the unit of the instrument. Thus, positive values less than 11% were considered an inefficiency of the DNIS since the intrarater standard error of measurement of the tibialis anterior muscle has a value of 11% (25).

### Statistical Analysis

The statistical analysis was performed using SPSS version 20.0 (IBM Corporation, Armonk, New York). The demographic and clinical variables of the study population were presented as mean and standard deviation

for continuous variables. Categorical variables were presented as absolute values and frequencies. Proportions of gender and physical exercise behaviour between groups were compared using the Chi-square test, whereas continuous variables were compared between groups with unpaired t-test. The normal distribution of the majority of the variables of the cardiac autonomic modulation was verified by the Shapiro-Wilk test. The comparison between groups according to the efficiency of the DNIS was performed by the unpaired t-test due to the parametric distribution of the variables. A significance level less than 5% ( $P < 0.05$ ) was considered for all analyses.

### RESULTS

Of the 58 patients who were included in the study, 56 completed all the assessments. One patient was excluded because of the presence of lymphedema in the arm that would be immersed in cold water, and for safety, the data collection of this subject was interrupted before the nociceptive stimulus of the CPT. In addition, the assessment of another patient was not complete due to technical problems with the heart rate monitor. In general, the sample showed a predominance of women (60%), physically active (55%), and classified as chronic pain (75%). Three patients presented more than one musculoskeletal diagnoses, 2 patients presented systemic hypertension; 2 patients presented gastric disease history; one patient presented diabetes mellitus; one patient presented hepatic disease history; one patient presented vascular disease history; one patient presented colitis history, and one patient presented dermatological problems. No significant differences were found between groups for age, gender, body mass index, physical exercise behavior, pain duration, and pain intensity measured by the NPRS between the groups. The study patient's characteristics are shown in Table 1.

Efficient DNIS was observed in 71% of patients in the forearm and 43% in the tibialis anterior. Table 2 provides the means and standard deviations of the PPT for both sites at baseline, after the CPT and the within-group change scores. The PPT in both sites was not significantly different among groups at baseline. The unpaired t-tests revealed that both the mean PPT values and within-group change at both testing sites of patients with impaired DNIS were significantly lower than those with normal DNIS ( $P < 0.01$  each).

The normal DNIS group presented greater HRV than the impaired DNIS group. The unpaired t-test showed

Table 1. Demographic and clinical characteristics of the patients with musculoskeletal pain (n = 56).

Characteristics	Impaired DNIS (n = 14)	Normal DNIS (n = 42)	P value
Age (years)	47.57 (15.17)	41.33 (13.51)	0.186
Gender (Women), n (%)	11 (78.6)	24 (57.1)	0.151
Body mass index	26.22 (2.93)	25.99 (4.17)	0.826
Physical Exercise (Yes), n (%)	7 (50.0)	25 (59.5)	0.533
Comorbidities, n (%)	4 (30.8)	8 (19.0)	0.549
Pain duration (months)	28.75 (51.99)	39.69 (61.04)	0.520
Pain Intensity	5.57 (2.06)	5.33 (2.28)	0.719
Heart Rate (bpm)	73.42 (12.41)	67.91 (7.78)	0.137
Systolic BP (mmHg)	124.43 (12.8)	121.1 (16.83)	0.444
Diastolic BP (mmHg)	80.00 (9.35)	78.95 (13.14)	0.747

Note: Data are presented as mean (SD) for continuous variables and as frequency counts (%) for categorical variables. Significant differences between groups were tested using the unpaired t-test for continuous variables or the Chi-square test for categorical variables. Abbreviations: DNIS, descending nociceptive inhibitory system. Bpm, beats per minute.

statistically significant differences for the RMSSD ( $P = 0.02$ ), SDRR ( $P = 0.009$ ), LF ( $\text{ms}^2$ ) ( $P = 0.004$ ), HF ( $\text{ms}^2$ ) ( $P = 0.027$ ), and total power ( $P = 0.002$ ) (Fig. 1). There was no statistically significant difference for the other HRV variables (HF(n.u.), LF(n.u.), LF/HF) (Fig. 2) and for the BP response to the CPT (Fig. 3).

## Discussion

This study compared the cardiac autonomic response among patients with musculoskeletal pain with normal and impaired DNIS. The impairment of the DNIS has been considered as a marker of central pain sensitization, but its relation with the autonomic nervous system control of the heart has still not been fully understood. Our findings showed a significant reduction of the resting cardiac parasympathetic control in patients with impaired DNIS compared to patients with normal DNIS. Conversely, there was similar BP response elicited by the CPT, which is a proxy of the sympathetic responsiveness.

The deterioration of the cardiac parasympathetic regulation of the patients with impaired DNIS may be related to the central nervous system function modifica-

Table 2. PPT values for the dorsal forearm and the tibialis anterior sites of patients with musculoskeletal pain (n = 56).

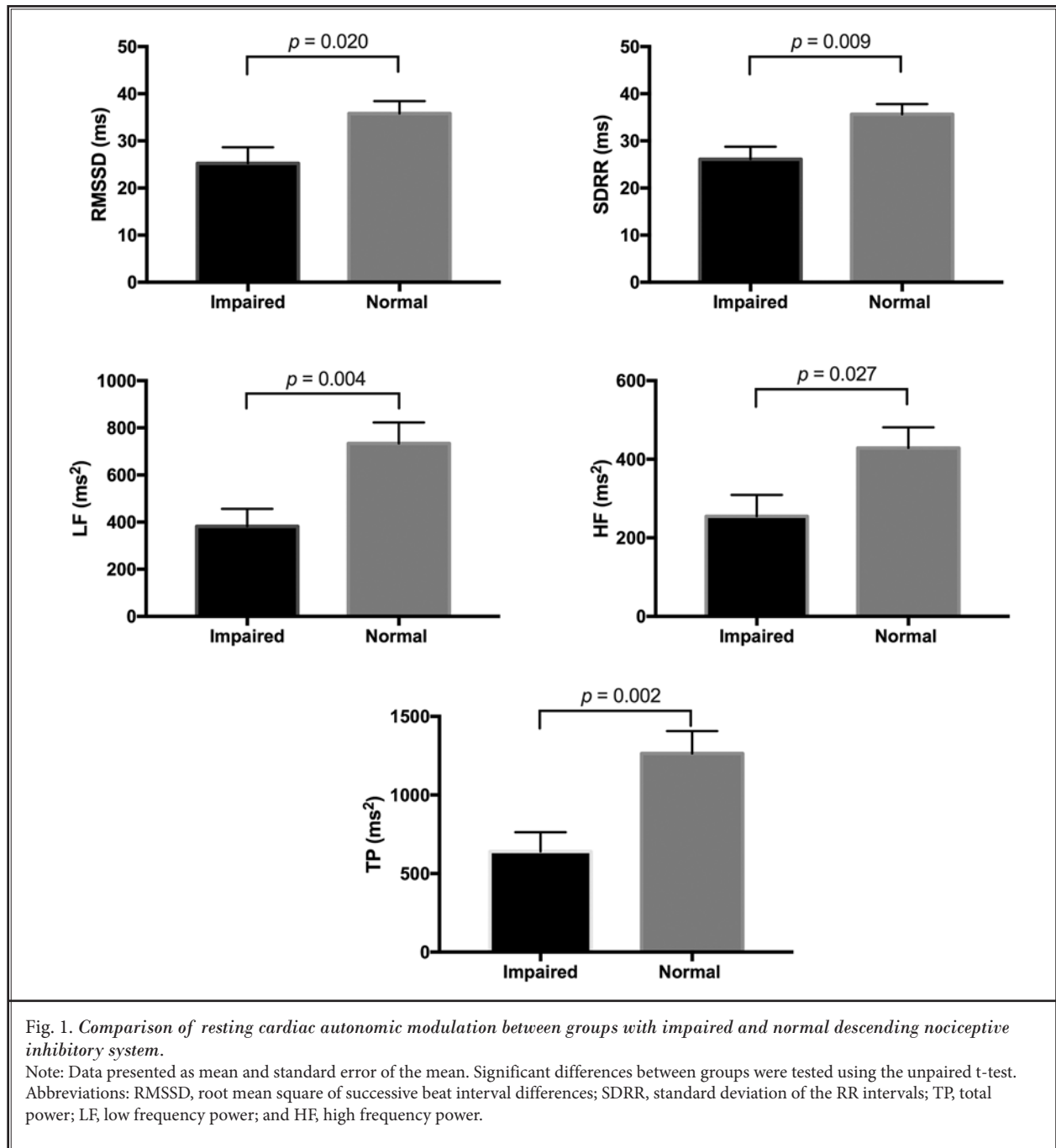
Characteristics	Impaired DNIS (n = 14)	Normal DNIS (n = 42)	P value
Baseline			
Dorsal forearm algometry (kgf)	3.63 (2.45)	3.62 (1.57)	0.993
Tibialis anterior algometry (kgf)	5.11 (3.05)	5.51 (2.19)	0.653
After CPT			
Dorsal forearm algometry (kgf)	3.64 (2.93)	6.15 (2.30)	0.009*
Tibialis anterior algometry (kgf)	4.63 (3.04)	7.41 (3.30)	0.008*
Within-group change			
Dorsal forearm algometry (kgf)	0.01 (0.80)	2.53 (1.27)	< 0.001*
Tibialis anterior algometry (kgf)	-0.48 (1.17)	1.89 (1.92)	< 0.001*

Note: Data are presented as mean (SD). Significant differences between groups were tested using the unpaired t-test. \*Represents significant  $P$ -values ( $P < 0.05$ ).

Abbreviations: DNIS, descending nociceptive inhibitory system. Kgf, kilogram-force.

tions. In patients with a whiplash injury, no association was observed between the parasympathetic branch and the CPM, although it was observed that patients with chronic injury showed correlations between HRV variables and the impairment of the endogenous analgesia (30). Data from neuroimaging studies demonstrate that chronic pain is associated with anatomical and functional modifications in different brain areas (31). It is also well recognized that brain areas involved in pain processing include more than sensory regions, but also cognitive and emotional areas such as amygdala, prefrontal cortex, insula, and anterior cingulate cortex (32). Therefore, it is plausible that alterations in the cognitive and emotional brain areas are related to HRV changes in patients with central sensitization.

The duration of pain was similar between the groups of the current study despite the differences observed in the HRV response. A decreased parasympathetic modulation in chronic pain has been clinically advocated, and it was recently confirmed by a systematic review. However, the authors of the systematic review pointed out that the results were strongly influenced by the data of patients with fibromyalgia (3). Autonomic



regulation of fibromyalgia is impaired by changing the sympathovagal balance, as well as the baroreflex system. Autonomic adjustment to acute stress is also impaired in this pathological condition (32,33). Although fibromyalgia is a chronic pain condition, possibly mech-

anisms associated with autonomic regulation are more related to central sensitization phenomenon than the duration of pain since pain chronicity is not decisive for the development of clinical presentation of central sensitization (8). This hypothesis is supported by a recent

study that also did not observe differences between the parasympathetic cardiac modulation at rest in patients with acute and chronic pain after a whiplash injury (30).

Painful stimuli and many pain conditions are related to enhancing of sympathetic activity (30,33-36). Indeed, the use of beta-blockade decreased pain intensity (33) and noradrenaline injection increased it (37). Since in our study all patients had pain, and there was no comparison with the asymptomatic population, it may be that the sympathetic activity was increased in both groups due to the symptom presence regardless of whether or not the pain was chronic, acute, or present inefficient endogenous analgesia. The lack of reference values for the autonomic variables makes it difficult to compare the groups with healthy data in the literature. The pain seems to act differently in the 2 segments of the autonomic nervous system. The parasympathetic system is related to the endogenous analgesia failure whereas the sympathetic system appears to respond directly to nociceptive stimuli because the central sensitization phenomenon does not interfere with its activation. These findings are important in individuals with musculoskeletal pain, and thus, clinicians are encouraged to consider alterations in the autonomic nervous system in addition to other traditional aspects, in the treatment of patients with pain, particularly those with inefficient DNIS.

The vast majority of the CPM studies assess one remote site solely to identify the DNIS impairment. However, we have assessed 2 distinct remote sites. Surprisingly, the 2 remote sites did not reveal a consistent response of the DNIS and this may be related to peripheral sensitization. Hence, we assumed that the patients with the inefficient DNIS at the 2 sites had an impaired DNIS while patients with contradictory results had normal functioning of DNIS. The variation observed in the HRV corroborates the distinction between the 2 groups. Further investigation on the response of the CPM in various remote sites should clarify the evidence of the specific groups according to the DNIS or the presence of confounders. Moreover, our findings highlight the requirement to research the CPM response in various remote sites since they can present distinct responses.

The CPM has been criticized concerning the recognition of pain patient subgroups (38), although the CPT has an excellent within-session reliability (21) and the CPM is compromised among chronic pain patients with multiple conditions (15). We used the distal dorsal forearm immersed in a bucket with cold water. Reason-

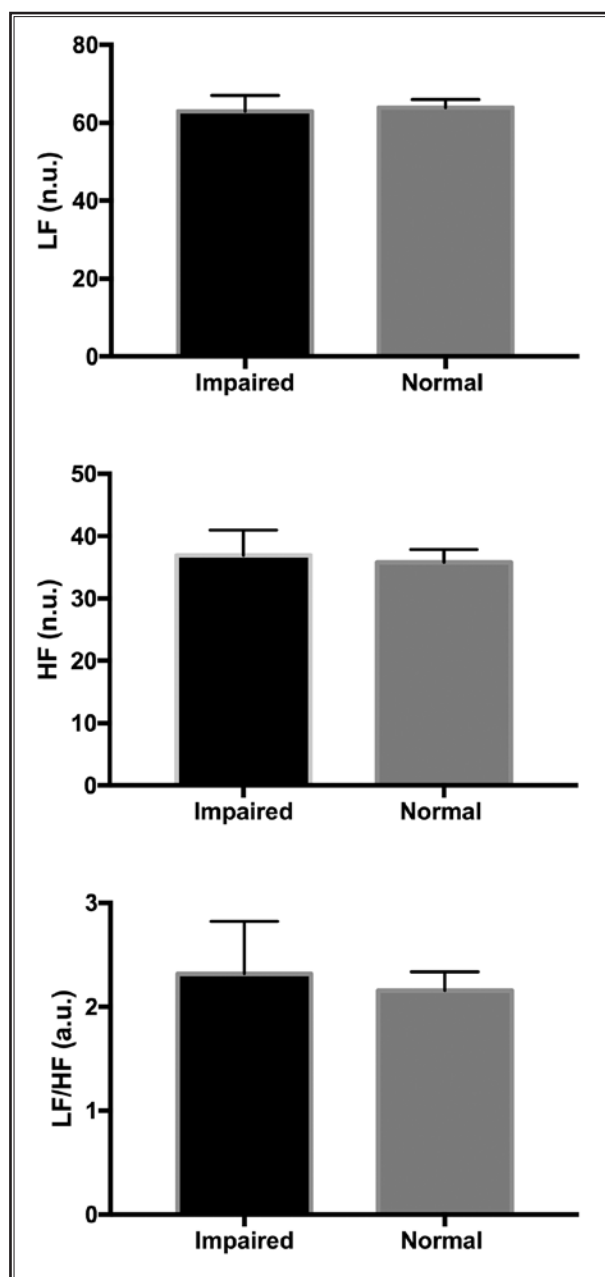
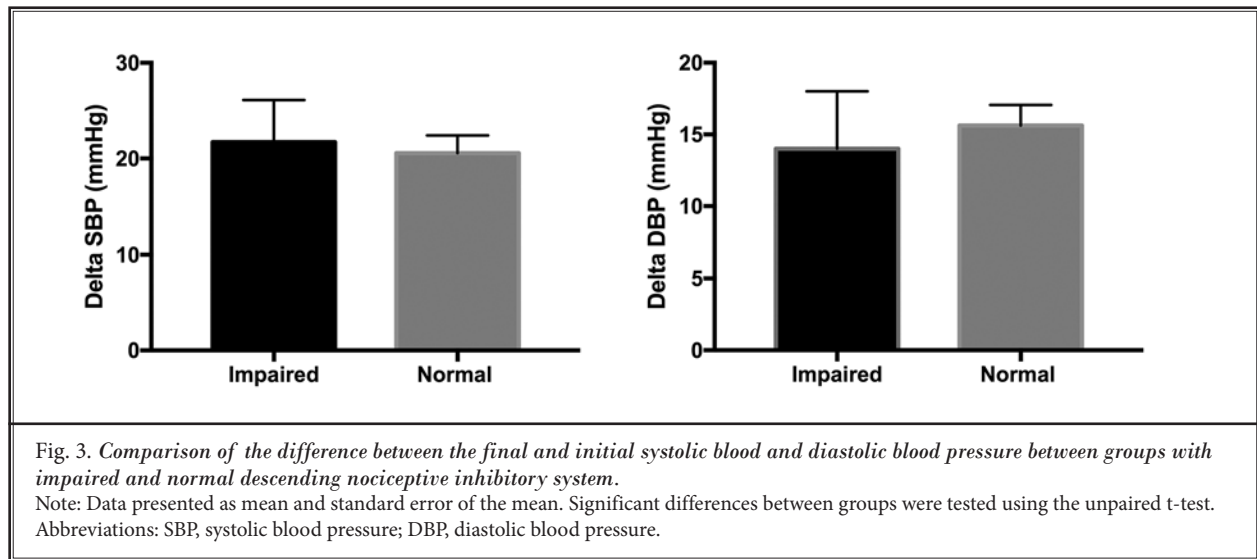


Fig. 2. Comparison of resting cardiac autonomic modulation between groups with impaired and normal descending nociceptive inhibitory system.

Note: Data presented as mean and standard error of the mean. Significant differences between groups were tested using the unpaired t-test.

Abbreviations: LF n.u., normalised low frequency power; HF n.u., normalised high frequency power; LF/HF, ratio between low and high frequency power (LF/HF).



ably, the segment immersed could contribute to the divergent response on the CPT. Moreover, we included patients with musculoskeletal pain regardless of structural damage or anatomic region. Thus, it is possible that patients with particular conditions may perform dissimilarly. The analysis of patients with musculoskeletal pain in homogenous conditions is encouraged by our findings.

We acknowledge some limitations. The small sample size limits the generalizability of the study findings albeit with similarities to the musculoskeletal pain populations previously described regarding middle-age adults (39), female predominance (39), overweight (40), sedentary lifestyle (41), moderate level of the pain intensity (42,43), and pain duration (43). All patients had musculoskeletal pain without considering the individual characteristics of each disease belonging to this population. Furthermore, there was no difference in the intensity of pain between the groups, diverging

from previous studies. The comparison with healthy individuals may also be a factor to be considered due to lack of reference values especially for the analysis of the sympathetic nervous system. Other factors such as physical exercise level, emotional changes, and visceral pathologies can alter the autonomic nervous system, making it difficult to directly establish relationships such as the complex system of pain modulation. Ultimately, we did not control the use of analgesic medication which may affect the CPM response despite the contradictory findings described in a systematic review (44).

## CONCLUSION

Patients with impaired DNIS presented lower resting HRV, indicating an altered vagal control of the heart. In contrast, the BP response to a sympathoexcitatory stimulus was preserved.



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