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Research Paper

Changes in Heart Rate Variability in Patients with Spleen-Qi Deficiency Syndrome

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Abstract
Many functional diseases are related to dysautonomia, and heart rate variability has been used to assess dysautonomia. However, heart rate variability has not been studied in Spleen-Qi deficiency syndrome (SQDS). Healthy volunteers (n = 37) and patients with SQDS (n = 67), recruited from the Clinic of the State University of Ecatepec Valley were included in the study. Outcome measures were average heart rate, standard deviation of the normal-to-normal heartbeat intervals, low frequency (LF), high frequency (HF) power, and the LF/HF ratio. Also, intestinal peristalsis, gastrointestinal symptoms (GSs), fatigue, and level of attention were measured. Standard deviation of the normal-to-normal heartbeat intervals (17 ± 2.3%) and HF (14 ± 3.1%) were lower in SQDS patients (17 ± 1.3%) than in healthy volunteers. SQDS patients had higher heart rate, LF power,

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syndrome

LF/HF ratio, and fatigue scores (9.6 ± 1.12%, 16 ± 2.1%, 22 ± 3.8%, and 21 ± 4.1%). The fatigue correlated positively with the LF/HF ratio and negatively with HF power. The SQDS group had lower concentration performance (16.2 ± 1.9%) in the d2 test. The intestinal peristalsis showed a reduction (15 ± 1.3%) as compared with control. GS score and peristalsis correlated negatively with HF. Our results suggest that the pathology of SDQS could be associated with a low vagal tone which causes a decrease in peristalsis, increased fatigue, reduced attention, and appearance of GSs.

1. Introduction

Traditional Chinese Medicine (TCM) is an ancient form of health care supported by systematic theories. It has been used as a preventive and therapeutic method for the treatment of a large spectrum of diseases. The diagnosis can be established by means of syndrome differentiation in the patient at a specific stage during the evolution of the disease. Syndrome differentiation is a useful method to prescribe therapies such as acupuncture, moxibustion, massage, and herbs and therefore, is a key procedure for the integration of basic theories of TCM with clinical practice [1]. However, syndrome differentiation is often subjective because of a lack of objective quantifiable variables [2] and usually depends on the practitioner's experience and interpretation of signs and symptoms [3,4]. To address this problem and to standardize the way in which symptoms are attributed to specific diseases and syndromes, in recent years several lines of research have analyzed the biomedical basis of signs and syndromes [5].

Within the framework of TCM, spleen-Qi deficiency syndrome (SQDS) is a very common syndrome, which is characterized by gastrointestinal impairment, immune alterations, poor memory, and decreased concentration [2,6]. Through the analysis of gene expression in patients with SQDS, a hypofunction has been reported in the expression of proteins and receptors that participate in innate immunity [2]. Alterations have also been detected in the digestive system such as a decrease in the concentration of motilin, gastrin, as well as in gastrointestinal motility [7]. In contrast, an increase in the rate of epithelial cell renewal because of a shortening of its half-life has also been reported [7]. Although the alterations mentioned above are part of the pathophysiology of different diseases, in TCM, it is often observed that Chinese syndromes apparently caused by different diseases may share the same biological basis [1].

The autonomic nervous system (ANS) regulates basic physiological processes, such as heart rate (HR), blood pressure, respiratory rate, gastrointestinal motility as well as the immune inflammatory response and cognition [8]. It is well known that alterations in the ANS are linked not only to gastrointestinal diseases such as inflammatory bowel disease [9] and functional dyspepsia [10] but also to diseases such as chronic fatigue syndrome [11,12], chronic obstructive pulmonary disease [13], kidney disease [14], cardiovascular disease [15] and hepatic diseases [16]. Because ANS is an important modulator of physiological functions and their dysfunction could be associated with gastrointestinal, immunological, and cognitive impairment, which are also reported in patients with SQDS, it is possible to suggest that SQDS reflects a sympathetic—vagal imbalance.

Through noninvasive techniques such as time domain and spectral analysis of heart rate variability (HRV), the activity of the ANS, and the contribution of its sympathetic and parasympathetic branches to cardiovascular control can be studied indirectly [17]. HRV is related to attention regulation, affective information processing, physiological flexibility, and cerebral blood flow [18]. Also, gastrointestinal motility, inflammation, perception, and cognition are regulated by the vagus nerve [19]. In addition, the spleen in TCM governs muscle, thought (level of concentration), blood, transport, and transformation of food into nutrients which are the sources of Qi, whereas blood provides nourishment to all organs and tissues of the body [7]. In accordance with the latter, we conjectured that patients with SQDS may present alterations in the sympathetic—vagal balance and consequently a reduction in gastrointestinal motility, increased fatigue, and a reduction in the level of attention. To address these issues, in the present contribution, we analyze HRV in the time domain using standard deviation of the normal-to-normal heartbeat intervals (SDNN) and in the frequency domain using low frequency (LF) power, high frequency (HF) power, and the LF/HF ratio, which were obtained using Fourier analysis. To analyze the possible association between changes in HRV and gastrointestinal symptoms and fatigue and attention, we also applied questionnaires such as the d2 test of attention, the fatigue impact scale (FIS), the gastrointestinal symptoms evaluation scale (GSRS), and the Pearson correlation coefficient (r) was calculated. We assume that analyzing such alterations will help us to better understand the underlying mechanisms of pathogenesis in Chinese Medicine, and a possible sympathetic—vagal dysfunction as assessed by HRV could be of relevance as a biomarker in syndrome differentiation such as SQDS.

2. Materials and methods

2.1. Ethical considerations

The research protocol followed the norms approved by the Ethics Committee of the State University Hospital of Ecatepec Valley (Act No.008-2016) in accordance with the ethical standards of the institutional and national research committee, the Helsinki declaration and its later amendments, and accepted ethical standards [20]. Before the beginning of the study, a signed informed consent form was obtained from all participants. Participants were previously informed of the objectives and characteristics

of the study. All authors declare that they have no conflicts of interests.

2.2. Study setting

This was a cross-sectional study conducted between august 2016 to July 2017, using a participant survey to collect data, from the Integrative University Clinic of the State University of Ecatepec Valley. Thirty-seven volunteers (20 women, 17 men) with average age of 52.5 $\pm$ 6.2 years (range 45—54 years; to avoid the influence of gender and age on primary and secondary outcomes) and 67 patients with SDQS (38 women, 29 men) with average age of 56.2 $\pm$ 4.3 years (range 46—58 years) were enrolled in the study. This was a pilot study in which the sample size corresponded to patients attended at the university hospital and who presented such a disease during the course of the enrollment.

Inclusion criteria: All participants were recruited from the Integrative University Clinic of the State University of Ecatepec Valley via advertisement and met the following inclusion criteria:

1. Patients with SQDS based on Guiding Principles of Clinical Research on TCM [21] in which the symptoms included:

(1) Primary Symptoms: (a) abdominal distension, (b) poor appetite, (c) loose stools or diarrhea, and (d) poor attention.
(2) Secondary Symptoms: (a) thinness, (b) weakness, and (c) weak blood pulse.
(3) Diagnostic criteria: having a pale tongue with a thin-white coating is essential for the diagnosis of SQDS. Patients were diagnosed with SQDS if he/she had a pale tongue together with two dominant symptoms or combined with one dominant and at least two secondary symptoms [22].

Syndrome differentiation was performed by two of the authors who are licensed acupuncturists, and inclusion criteria for the spleen deficiency group was checked by mean of a questionnaire containing data on TCM symptoms [22] followed by physical examinations, tongue examination, and pulse reading according to deficiency syndrome differentiation guidelines. In addition, gastrointestinal symptoms evaluation, D2 attention, and Bristol stool chart (designed to classify faeces into seven groups) also were used to complement the diagnosis for patient inclusion.

Exclusion criteria: Participants were excluded from the study if they had endocrine, psychiatric, infectious and/or inflammatory disease, structural digestive disease, or a clinical history of heart disease. Patients who refused to sign the informed consent form were automatically excluded from the study.

2.3. Electrophysiological recordings

Intestinal peristalsis was evaluated by means of surface electrogastrography. Surface electrocardiography was used for subsequent analysis of HRV. To avoid the influence of circadian fluctuations, the electrogastrography and electrocardiography monitoring were realized simultaneously in the same session and time of the day for all patients (between 9.00 a.m. and 11.00 a.m), in a quiet examination room with a constant ambient temperature (25°C). All participants maintained a seated position during the rest and monitoring intervals in an adjustable examination chair with knee and trunk-thigh angles of 120 and 135°, respectively.

2.3.1. Electrocardiogram and heart rate variability

Electrocardiogram (ECG) signals were recorded for 5 minutes after a 10-minute rest. First, the skin of each subject was cleaned at the level of the xiphoid process and the chest. Throughout the examination, the ECG signals were collected on-line via three electrodes attached to the chest and connected to a MP150 Biopac Digital System (USA). The 5-minute ECG segments of all patients were amplified, digitized, and stored on a computer. The MP150 Biopac had a sensitivity of 250 μV and a sampling frequency of 256 Hz with a measurable range of HR of 35—250 beats per minute (bpm). Only normal-to-normal (N-N) heartbeat intervals were included for statistical analysis. The N-N intervals were visually inspected for artifacts, and intervals less than 0.4 sec (HR $>$ 150 bpm) or larger than 1.5 sec (HR $<$ 40 bpm) were identified, and ectopic beats were replaced with interpolated N-N interval values. ECG traces with more than 1% of ectopic beats were excluded from further analysis. Recorded data were transferred to the Kubios HRV analysis software (version 2.2, Matlab Kuopio, Finland [23]). Time domain and frequency domain indices were calculated for the time series of N-N intervals. Time-domain indices included average HR and SDNN. Frequency domain measures included LF power, defined as the energy in the power spectrum between 0.04 and 0.15 Hz, and HF power, defined as the energy in the power spectrum between 0.15 and 0.40 Hz. LF and HF were taken as indices of sympathetic and parasympathetic nerve activity, respectively, and the LF/HF ratio as an index of the sympathovagal balance. These parameters are recommended by the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [24] and provide an understanding of the effects of the sympathovagal modulation of HR.

2.3.2. Electrogastrogram

Electrogastrogram (EGG) signals were passed through 0.016 Hz high-pass filter and a 0.25 Hz low-pass filter and were recorded for 30 minutes after a 10-minute rest. The EGG signal was reviewed to remove artifacts, and the resulting EGG signal was digitized for computer analysis and subjected to a fast Fourier transform to extract the frequency information. A running spectral analysis of the wave form was applied, with particular interest for the percent power in the frequency ranges of 1.0 to 2.5 cpm, 2.5 to 3.7 cpm, and 3.7 to 10 cpm.

2.4. Questionnaires

2.4.1. Cognitive tests

The d2 test of attention is a paper-and-pencil cancellation task that measures distractibility, selective

attention, and sustained attention [25,26]. The participant is presented with rows consisting of the letters "d" and "p" with varying numbers of marks surrounding the letters. The participant is instructed to only mark the letter "d" that has two marks and to ignore all other stimuli. Four parameters of the d2 test were assessed: percentage of errors, total number of items minus error scores, the fluctuation rate, and concentration performance (the number of successful d2 items minus omission errors).

2.4.2. Fatigue test

The FIS was developed to assess the symptoms of fatigue as part of an underlying chronic disease or condition [27,28]. We used the Spanish translation and validated version for a Mexican population of the FIS, with 10 item Likert scale. The response key for each item was a 5-point scale ranging from "0 = no problem" to "4 = extreme problem" the total score of each item was the level of fatigue organized into three physical, mental, and psychosocial dimensions. The Cronbach α levels for the FIS are 0.81—0.9728.

2.4.3. Gastrointestinal symptoms evaluation

The GSRS was used as a specific instrument for the measurement of gastrointestinal disease and includes 15 items grouped according to different gastrointestinal symptoms: reflux, abdominal pain, indigestion, diarrhea, and constipation. It has a score based on a Likert scale of 7, where 1 represents the most favorable result and 7 the most negative.

2.5. Laboratory measurements

Fasting serum total cholesterol, triglycerides, glucose (lot no.: B302, Konelab; Thermo Fisher Scientific Inc., Vantaa, Finland) and concentrations were measured enzymatically using an automatic analyzer (Konelab 60i). Total cholesterol (lot no.: B540, Konelab) and triglycerides (lot no.: C186, Konelab) were measured by enzymatic colorimetric tests.

2.6. Statistical analysis

A descriptive analysis of the quantitative variables obtained by the ECG was performed for the whole population by determining the average and standard deviation (±SD) and expressed in percent values (%) with respect to healthy volunteers. A parametric Student *t* test or a non-parametric Wilcoxon test was used to quantitatively compare variables according to distribution characteristics. A Student *t* test or Chi-square test was used to determine the differences of the demographic and biochemical parameters between the two groups. Pearson's correlation coefficient (r) was used to assess the degree of relation between the quantitative parameters obtained from HRV, fatigue scores, d2 attention test, and gastrointestinal symptoms. All statistical analyses

Table 1 Baseline data of the healthy control group and the patient group with SQDS. Shown are average values ± standard deviation.

Characteristic	Controls (n = 37)	SQDS (n = 67)	*p* (#p > 0.05)
Demographics			
Age (years)	52.5 ± 6.2	56.2 ± 4.3	#
Sex ratio (male/female)	12/25	23/44	#
Weight (kg)	67.6 ± 12.8	71.4 ± 8.1	#
Height (meters)	1.6 ± 0.19	1.5 ± 0.08	#
Body mass index (kg/m2)	27 ± 4.8	26 ± 3.2	#
Body fat (%)	41 ± 8.7	31 ± 11.6	#
Visceral fat (%)	10.5 ± 2.8	9.9 ± 3.4	#
Basal metabolism (Kcal)	1349 ± 164	1443 ± 229	#
Skeletal muscle (%)	25.2 ± 6.2	29.4 ± 5.8	#
Metabolic age (years)	59 ± 13.38	62.2 ± 13.8	#
Pulse	65 ± 9.9	70 ± 9.9	#
Biochemicals			
Triglycerides (mg/dl)	165 ± 38	182 ± 45	#
Cholesterol (mg/dl)	216 ± 44	186 ± 42	#
Glucose (mg/dl)	95 ± 17	99 ± 20	#
Lifestyle factors			
Smoking			
No	34 (91.9%)	65 (97.1%)	#
Yes	3 (8.1%)	2 (2.9%)	#
Alcohol consumption			
No	30 (81%)	56 (83%)	#
Yes	7 (19%)	11 (17%)	#
Physical exercise			
Never or moderate	34 (91.9%)	63 (94%)	#
Frequently	3 (8.1%)	4 (6%)	#

SQDS = Spleen-Qi deficiency syndrome.

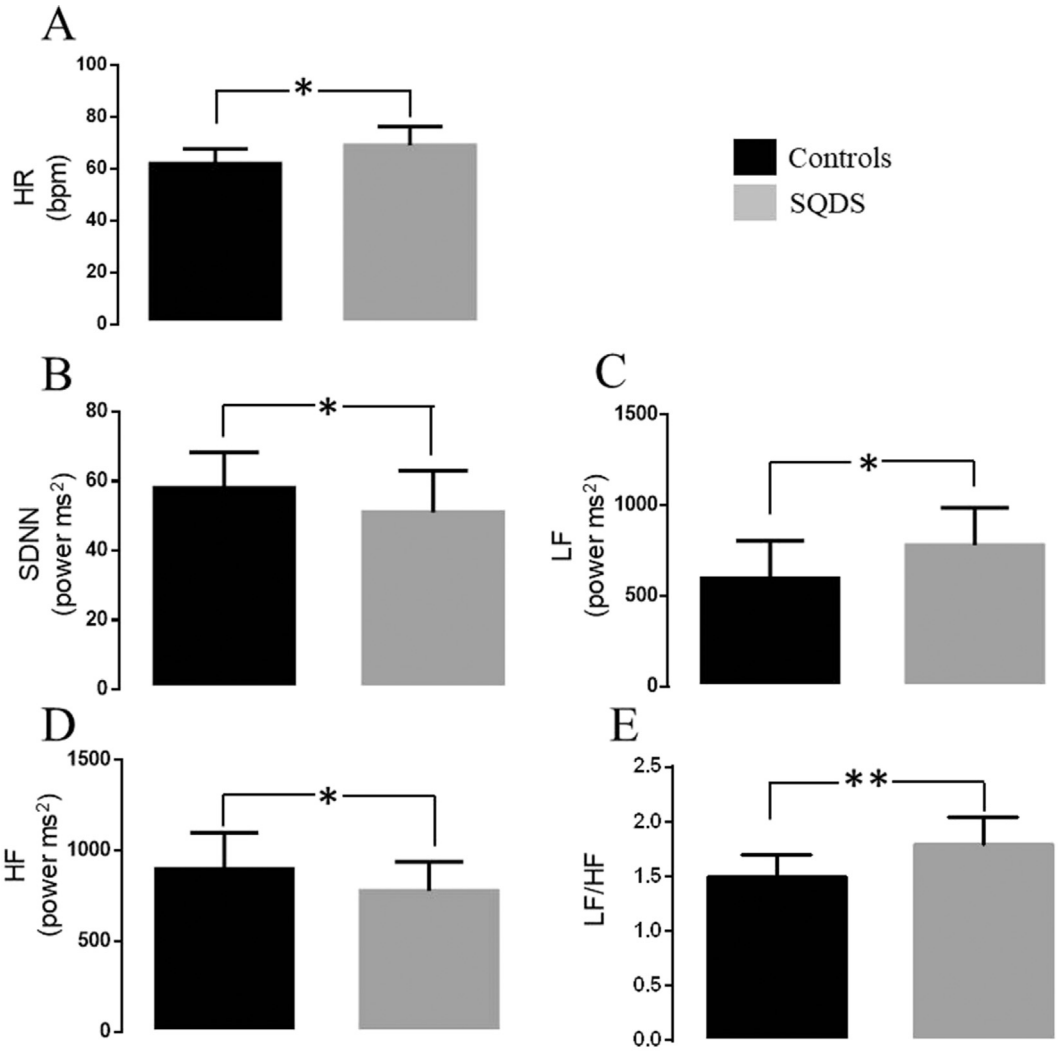

Figure 1 Graphs indicating average values ± standard deviation (SD) of average heart rate and heart rate variability parameters in healthy controls (n = 37) and patients with Spleen-Qi deficiency syndrome (SQDS, n = 67). (A) Average heart rate (HR). (B) Standard deviation of normal-to-normal heartbeat intervals (SDNN). (C) Low frequency power (LF). (D) High frequency(HF) power. (E) LF/HF ratio. Bars indicate *$p < 0.05$, **$p < 0.01$.

were performed by blinded biostatisticians using Graph-Pad Prism (version 5, San Diego, CA) software. A value $p < 0.05$ of less was considered statistically significant.

3. Results

3.1. Characteristics of participants

The general characteristics of the study participants are shown in Table 1. Of 104 participants, 37 were healthy, and 67 had a diagnosis of SQDS. No significant differences in age, sex, height, weight, metabolic age, education level, occupation, marital status, meal regularity, exercise, smoking, or use of alcohol ($p > 0.05$) were observed between groups. Metabolic characteristics such as triglycerides, cholesterol, and glucose levels neither showed significant differences ($p > 0.05$).

3.2. HR and HRV parameters

Fig. 1 compares the group-averaged HR and HRV parameters for the healthy controls and the SQDS patients. There was a small but significant increase in HR in the SQDS patients with respect to the healthy volunteers ($p < 0.05$; Fig. 1A). SDNN values were significantly lower in SQDS patients than in healthy volunteers ($p < 0.05$; Fig. 1B), whereas LF and LF/HF parameters were significantly higher ($p < 0.05$; $p < 0.01$; respectively; Fig. 1C and E). In contrast, HF was lower in SQDS patients than in healthy volunteers ($p < 0.05$; Fig. 1D).

3.3. Fatigue

There was a significant increase in fatigue as determined by the FIS score in SQDS patients as compared with healthy individuals ($p < 0.01$; Fig. 2A).

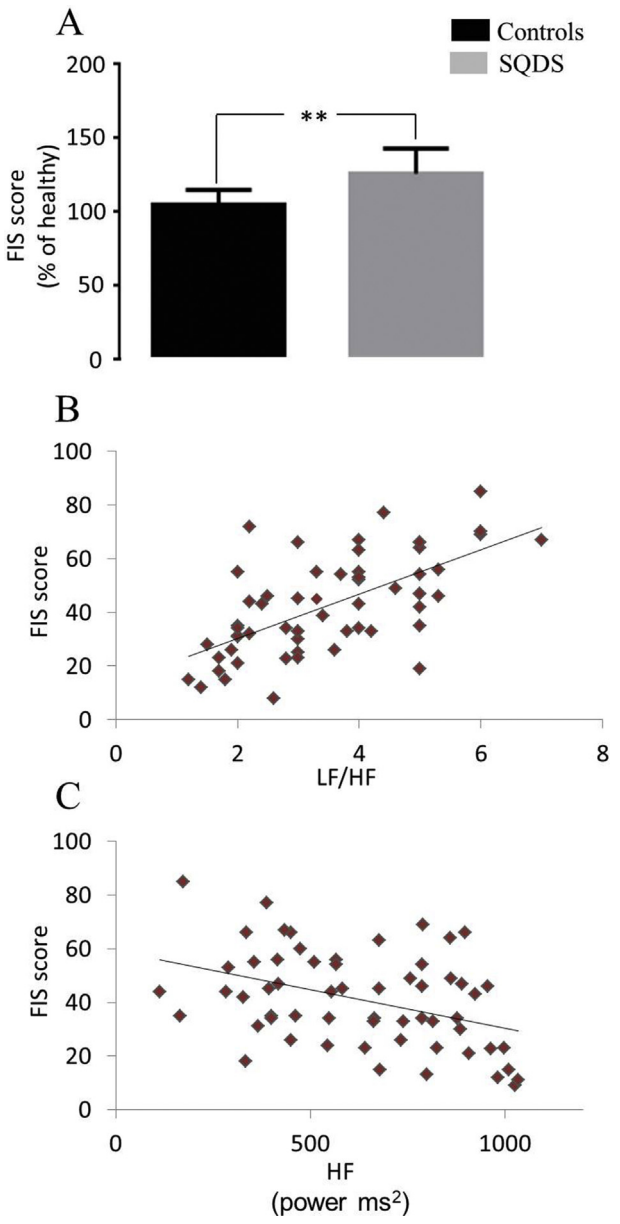

Figure 2 Correlation between percentage of fatigue impact scale (FIS) score and parameters of heart rate variability (HRV). (A) Percentage of fatigue impact scale (FIS) score in healthy controls and patients with Spleen-Qi deficiency syndrome (SQDS). (B) Relation between FIS and low frequency/high frequency power index (LF/HF) score in patients with SQDS syndrome (n = 67). (C) Relation between FIS and high frequency power index (HF). $^{**}p < 0.01$.

3.4. HRV parameters and their relation with the level of fatigue

Fig. 2B illustrates the possible relationship between FIS scores and LF/HF values (HRV parameters) obtained from patients with SQDS and healthy volunteers. Both parameters seem to follow a linear relationship, with positive correlation ($r = 0.48$). On the other hand, fatigue scores and HF values are negatively correlated ($r = -0.37$) in patients with SQDS (Fig. 2C).

3.5. Gastrointestinal symptoms

Fig. 3A–F shows the averaged values of several gastrointestinal symptoms (GSRS) such as abdominal pain, reflux, diarrhea, indigestion, and constipation in patients diagnosed with SQDS and healthy participants. The scores of abdominal pain, indigestion, and constipation were all higher ($18 \pm 3.2\%$, $16 \pm 22\%$, and $22 \pm 3.8\%$, respectively) in patients with SQDS than in healthy volunteers ($p < 0.05$). No significant differences were found for reflux and diarrhea.

3.6. Intestinal peristalsis

Fig. 4A shows normalized values as a percentage of the intestinal peristalsis recorded in both healthy subjects and patients with SQDS. There was a significant reduction ($15 \pm 1.3\%$) in peristalsis recorded in patients with SQDS compared with that recorded in control subjects ($p < 0.05$).

3.7. HRV parameters and correlation with level of gastrointestinal symptoms and peristalsis

The possible relationships between gastrointestinal scores and HRV parameters are presented in Fig. 4 (panels B and C). Gastrointestinal symptoms scores and HF exhibit a linear relationship with negative correlation (Fig. 4B, $r = -0.45$). Peristalsis also appears to be negatively correlated with HF (Fig. 4C, $r = -0.42$).

3.8. Cognitive analysis

Fig. 5 (panels A to D) shows the averaged values (±SD) of the parameters measured during the d2 test. As illustrated in panels A, B, and C, the SQDS group had significantly more errors ($22.8 \pm 3.3\%$; $p = 0.014$), higher percentage of errors ($17.3 \pm 1.4\%$; $p = 0.015$), and significantly higher fluctuation rate in the d2 test than the healthy group control group ($18.11 \pm 2.5\%$; $p = 0.019$, respectively). Meanwhile, the SQDS group showed a significantly lower concentration performance in the d2 test than the controls ($16.2 \pm 1.9\%$; $p = 0.022$; panel D).

4. Discussion

SQDS is a multisystem functional impairment that reflects several digestive tract disturbances and imbalances in the immune system [2]. Despite the fact that syndromes have been used for many years in TCM, there is little evidence on their physiological nature. In the present study, for the first time, we evaluate the function of the autonomous nervous system in SQDS patients by means of noninvasive measures based on HRV. We found that patients with SQDS have a significantly reduced SDNN, reduced HF, increased LF, and an increased LF/HF ratio in comparison to healthy volunteers. LF power is considered to be a strong indicator of HR modulation by the sympathetic nervous system, whereas HF is attributed mainly to parasympathetic activity. The LF/HF ratio is interpreted as a measure of sympathetic–vagal balance [17], where larger values reflect a dominance of the sympathetic

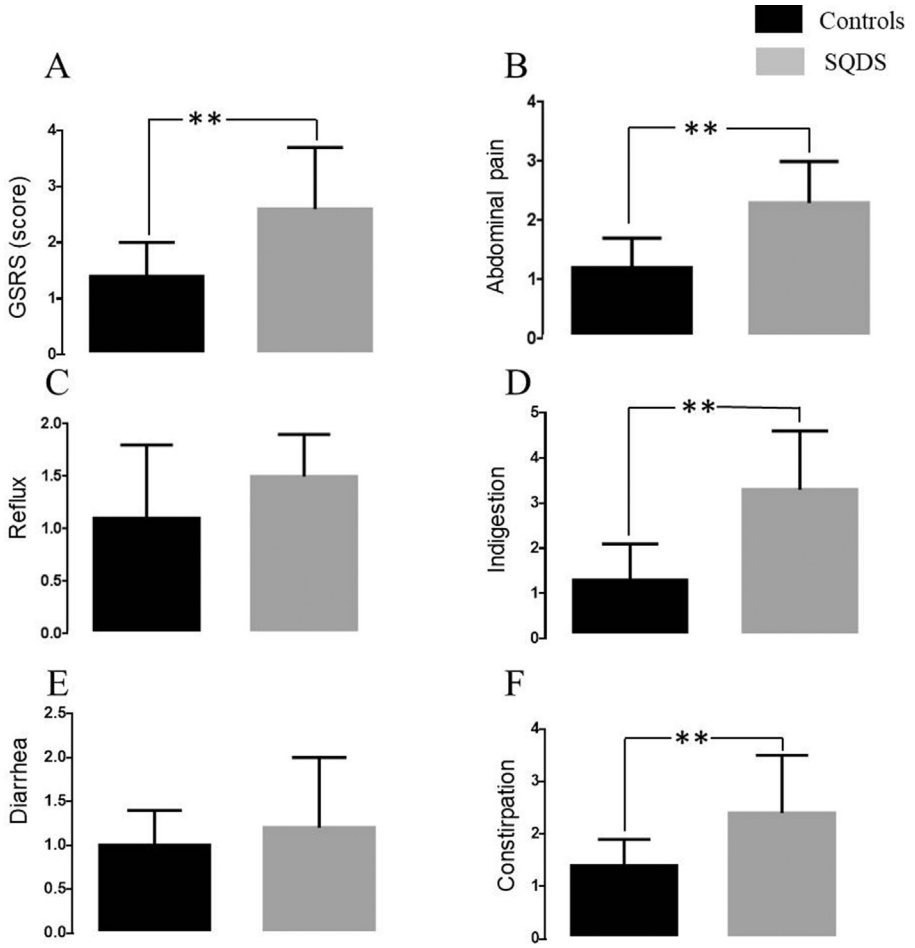

Figure 3 Average values ± standard deviation (±SD) of the scores obtained with the gastrointestinal symptoms evaluation scale (GSRS) in healthy controls (n = 37) and patients with SQDS (n = 67). (A) Total gastrointestinal symptoms score, (B) level of abdominal pain, (C) reflux, (D) indigestion, (E) diarrhea, and (F) constipation, $^{**}p < 0.01$.

system, and smaller values reflect the low activity of the sympathetic and/or large activity of the parasympathetic system. Our study showed an increase of the LF component and a decrease of the HF component in SQDS patients. Thus, it seems reasonable to propose that SQDS is associated to alterations in the sympathetic—vagal balance, with low vagal and or/dominant sympathetic tone.

4.1. Fatigue

In some studies, it has been shown that patients with chronic fatigue exhibit alterations in the ANS. In particular, an increase in the average HR, a decrease in LF power, as well as a reduction of the total variability (SDNN) has been reported, which suggests a predominance of the sympathetic state of the ANS [29]. In the present study, we found that patients with SDQS present an increase of the degree of fatigue as compared with the control group, and these alterations correlate with reduced HF power. It is possible that the fatigue present in patients with SDQS is associated with a reduced functioning of the cholinergic system and an increased sympathetic tone. Likewise, fatigue in the SQDS patients correlates positively with the LF/HF ratio and negatively with HF power. Our findings are suggestive of a relation in SDQS patients between fatigue on the one hand and an increase in sympathetic tone and/or a decrease of the parasympathetic tone on the other hand.

4.2. Gastrointestinal symptoms

In this study, we found that abdominal pain, indigestion, and constipation were all higher in patients with SQDS than in healthy volunteers. It was previously reported that patients with functional digestive dyspepsia have a decreased parasympathetic activity or vagal tone [30,31]. Vagal dysfunction is also known to contribute to esophageal hypomotility, decreased gastric tone, and gastrointestinal motility [19]. In addition, we also found that gastrointestinal symptom scores are negatively correlated with HF power of HRV. Consequently, it would appear that gastrointestinal symptoms such as indigestion and constipation are caused at least in part by a low vagal tone in patients with SQDS.

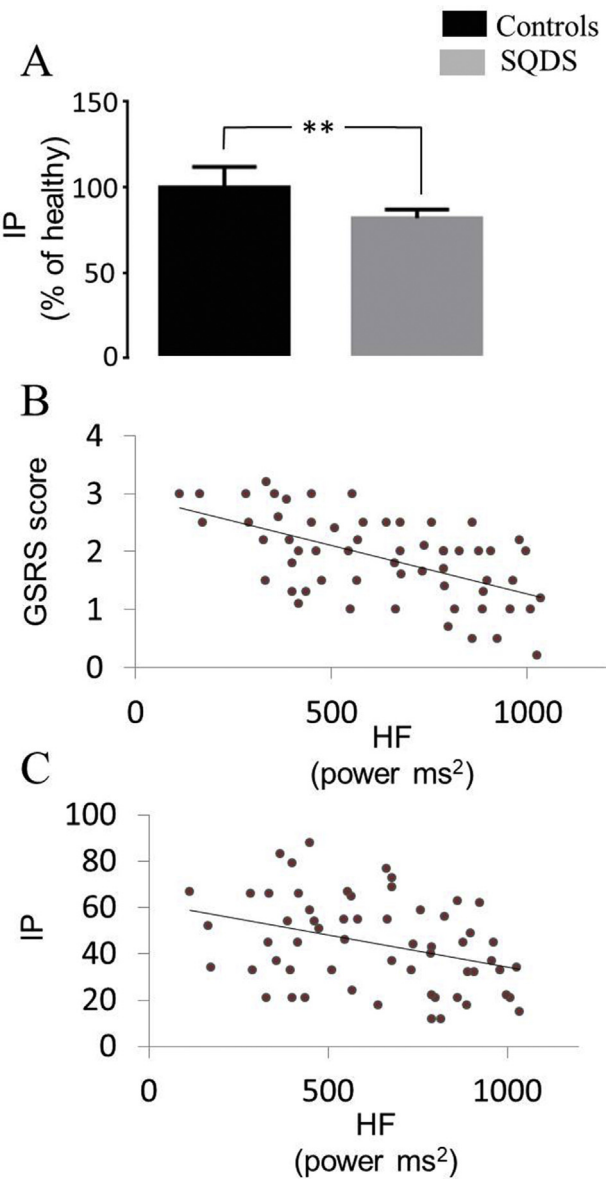

Figure 4 Correlation between gastrointestinal parameters and high-frequency power of heart rate variability (HRV). (A) Intestinal peristalsis (IP) recorded in healthy controls (n = 37) and patients with SQDS (n = 67). The data are expressed in normalized percent values (%) relative to those recorded in healthy subjects (100%). (B) Relationship between high frequency power (HF) of heart rate variability (HRV) and gastrointestinal symptoms score (GSRS) in patients with SQDS (n = 67). (C) Relationship between HF power of HRV with intestinal peristalsis (IP) in patients under SQDS. $^{**}p < 0.01$.

4.3. The vagus nerve and attention

Attention is a complex cognitive function, which enables an individual to select out of numerous stimuli those which at a given moment may be regarded as more important or more interesting, allowing to dedicate more processing time to these particular stimuli. In the present study, we found that patients with SDQS committed more mistakes by omission or by incorrect crossing out than the healthy subjects in the d2 cognition test. Previous studies also have reported attention deficits in patients with intestinal bowel diseases [32]. Possible cognitive impairments have been associated with increments of serum cytokines during concentration, with longer time response in cognitive tasks, as detected in elderly populations and patients with systemic inflammation such as Crohn's disease [33]. The vagus nerve contributes to the bidirectional interaction between the brain and the digestive system and forms part of the brain–gut axis. In addition, the vagus nerve modulates gastrointestinal motility [19] and inflammation through the cholinergic antiinflammatory pathway [34]. There is growing evidence for the relevant role of the vagus nerve in the regulation of physiological, affective, cognitive, behavioral, and emotional reactivity [35]. As an example, vagus nerve stimulation improves working memory performance in humans [34], creative processes, and response inhibition in healthy individuals [33] and modulates flow experience [36]. Flow experience has been described as an increase of concentration and attention levels and an enhanced sense of control without keeping track of time [37]. Therefore, we suggest that a reduction in the vagal tone could be an important factor to explain the reduced level of attention of patients with SDQS.

4.4. Intestinal peristalsis

It is well known that gastrointestinal motility is regulated by central and peripheral mechanisms; in particular, cholinergic mechanisms increase gastrointestinal motility. In our study, we found that patients with SDQS showed a decreased intestinal peristalsis as measured by EGG and which correlates with the reduced HF power in HRV (Fig. 4A and C).

It may be argued that the reduction in intestinal motility is related to an alteration in the parasympathetic activity of patients with SDQS, and it has been proposed that the decrease in vagal tone is associated with mental stress and personality factors [38]. It has also been shown that medial prefrontal cortex activity is inversely associated with activity of the amygdala which innervates central autonomic network areas, and it is involved in the modulation of startle responses such as stress. In this sense, studies have shown that when the prefrontal cortex is inhibited, by means of pharmacological intervention, the activity of the cardioaccelerator circuit increases and vagal activity decreases [18]. By means of novel questionnaires for TCM pattern diagnosis of stress [39], it has been shown that of 45 females with SDQS, almost 55.15% presented chronic stress, and of 16 males with SDQS, 54.81% also present chronic stress. In addition, it has been shown that decreased HRV at rest reflects a low vagal tone and can be considered as a marker of stress [40]. In our study, we also found a reduction in HRV (as evidenced by a reduction in SDNN) in patients with SDQS. Therefore, it is possible that low peristalsis and reduced cholinergic activity are associated with stress and also may be an important causal factor for the reduced level of attention in patients with SDQS.

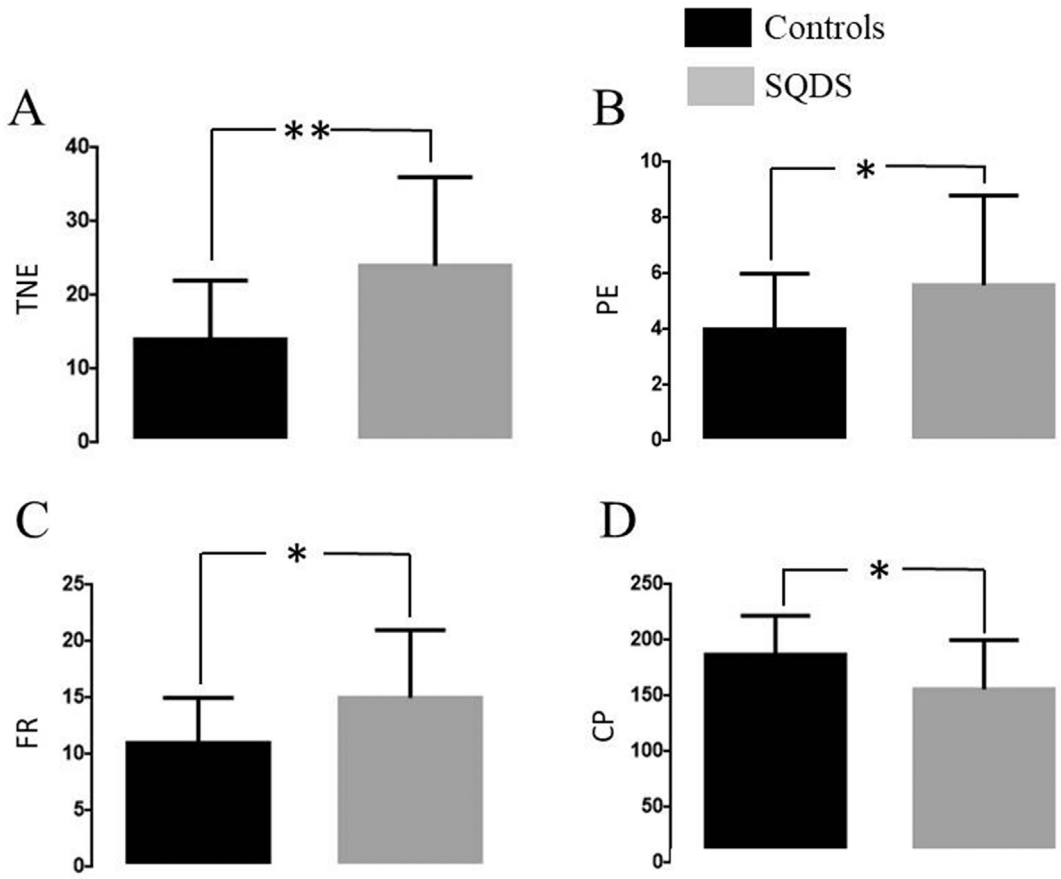

Figure 5 Average values (±SD) of different parameters measured by the d2 attention test in healthy volunteers (n = 37) and patients with SQDS (n = 67). (A) Total number of errors (TNE). (B) Percentage of errors (PE). (C) Fluctuation rate (FR), (D) Concentration performance (CP). *$p < 0.05$, **$p < 0.01$.

4.5. Can HRV be used as a marker in emotion, health, and spleen-Qi syndrome differentiation?

Different studies have reported the importance of HRV in emotion and health. Decreased HRV is related to several diseases, such diabetes and obesity [40]. A reduction in HRV is also associated with psychological symptoms of poor concentration, ineffective emotional regulation, behavioral inflexibility [41], depression [42], generalized anxiety disorder [43], and posttraumatic stress disorder [44]. In addition, a positive correlation was found between prefrontal cortex blood flow and SDNN and LF/HF indices of HRV [44,45]. A structural link has been proposed between psychological processes such as emotion and cognitive regulation on the one hand and health-related physiological processes on the other hand, and this circuit can be quantified with HRV [40].

In TCM, a syndrome may include both physical and psychological impairment. In the case of SQDS, pathological changes are characterized by Qi deficiency with impaired transportation and transforming function of the spleen [7], leading to low energy and blood to all organs and tissues, and resulting in fatigue. Gastrointestinal disorders could lead to altered eating habits that might reduce the total energy intake [46,47]. Resting metabolic rate is known to decrease in response to restriction of energy intake [48]. In addition, Mun et al. [46] found that patients with SDQS have low resting metabolic rate, and this could be associated to an impairment in the transportation and transforming function of spleen. SQDS is also characterized by gastrointestinal impairment, such as irregular defecation, reduced bowel movement, indigestion, dyspepsia, and fatigue [46], symptoms that may be associated with reduced vagal tone and that are evidenced by low HRV. In addition, from the TCM perspective, spleen governs thought, in which brain activities depend on the availability of nutrients, Qi (energy), and blood. With adequate Qi, blood and normal function of spleen—stomach, brain activities can proceed normally. In contrast, a deficiency of spleen-Qi leads to an impairment in cognitive function, such as poor memory or a reduced concentration capacity, as evidenced in the present study by means of the d2 cognition test.

The microbiota, the gut, and the brain communicate in a bidirectional way through the ANS and the circumventricular organs [19]. It has been shown that the microbiota-gut axis is involved in the pathophysiology of chronic and neurodegenerative disorders [49]. Our observation of reduced SDNN and HF indices of HRV in SQDS patients may be evidence for a possible impairment of the gut—brain axis, and it is possible that the low vagal tone is in part responsible for the gastrointestinal symptoms, fatigue, and poor attention in patients with SQDS.

In conclusion, the pathology in patients with SDQS could be associated with a sympathetic—vagal imbalance, with low vagal tone, which produces a diminished peristalsis, increased fatigue, reduced attention, and gastrointestinal disorders. It is recommended that further studies with a significant sample be conducted to establish that sympathovagal dysfunction could be assessed by HRV and considering as biomarker in the differentiation of TCM syndromes such as SQDS.

Disclosure statement

None of the authors have conflict of interest regarding this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jams.2019.07.002.

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